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Multimodality Treatment of Oesophageal Cancer:

Effects and Side Effects

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Multimodality treatment of oesophageal cancer: effects and side effects

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Claes Johan, my husband, without whom many of the figures in this book would not exist.

To Felicia and Nathan, who probably will never read this book, but hopefully will experience a world full of wisdom.

ABSTRACT

Background
Oesophageal cancer is highly fatal and treatment with curative intent is beset with many side effects. Treatment options are (1) chemoradiotherapy, (2) chemotherapy with or without the addition of radiotherapy followed by surgery or (3) surgery alone. The aims of this thesis are to evaluate outcome and side effects from neoadjuvant treatment followed by surgery and from definitive chemoradiotherapy in combination with cetuximab.

Patients and methods
NeoRes I is a prospective, randomised, multicentre trial reported in Papers I and II. Patients with resectable oesophageal cancer were randomly allocated to receive three 21-days cycles of cisplatin and fluorouracil with or without the addition of radiotherapy to 40 Gy followed by oesophageal resection.

In Paper III the effects on cardiac exercise test and on pulmonary function after neoadjuvant treatment and 1-2 years after surgery were investigated in a cohort of 97 patients included in the NeoRes I trial.

LERFOX-C is a prospective, non-randomised, multicentre trial reported in Paper IV. Eligible patients had localized oesophageal cancer not suitable for surgery. Treatment consisted of radiotherapy to 50 Gy concurrent with weekly cetuximab and three 21-days cycles of oxaliplatin and fluorouracil.

Results
In papers I and II, 181 patients were included. All three chemotherapy cycles were delivered to 73% of the patients allocated to chemoradiotherapy and to 86% of those allocated to chemotherapy. 87% of those allocated to chemoradiotherapy received at least 30 Gy. 87% in the chemoradiotherapy group and 86% in the chemotherapy group underwent tumour resection. Tumour response was better among those allocated to chemoradiotherapy with fewer metastatic lymph nodes at resection, a higher rate of radical resection and a higher rate of complete histopathological response (28% versus 9%), but 5-year overall survival was similar (42% versus 40%).

In Paper III we found a slight decrease in vital capacity and forced expiratory volume in 1 second after neoadjuvant treatment, and a more profound decrease 1-2 years after surgery. Maximum exercise capacity decreased after neoadjuvant treatment and persisted and 1-2 years after surgery. We did not find any significant differences between the treatment groups.

In Paper IV, 51 patients were eligible for survival analysis and 46 were eligible for toxicity and recurrence analysis. Full radiotherapy dose was delivered to 80%, 75% received all three cycles of chemotherapy and 73% received four or more doses of cetuximab. Within six months from the end of treatment, six patients died from complications from fistulas between the oesophagus and aorta or airways. The estimated loco-regional progression-free survival at one year was 47%. Overall survival at three years was 29%.

Conclusions
The addition of radiotherapy to neoadjuvant chemotherapy increases tumour response in patients with localized, resectable oesophageal cancer without affecting patterns of recurrence or survival. Multimodality treatment causes short-term and long-lasting impairment in pulmonary function and exercise capacity. Oxaliplatin and fluorouracil given concurrent with radiotherapy and cetuximab is well tolerated and has a curative potential in the treatment of localized oesophageal cancer. However, results from recent phase III trials do not support the addition of cetuximab and cannot be recommended as standard of care.

LIST OF SCIENTIFIC PAPERS

I. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction.
Annals of Oncology 27:660-667, 2016

II. Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus or gastro-esophageal junction. Long-term results of a randomized clinical trial.
Diseases of the Esophagus, 2018

III. Pulmonary function and cardiac stress test after multimodality treatment of esophageal cancer.
Practical Radiation Oncology 6:e53-e59, 2016

IV. Definitive chemoradiotherapy with oxaliplatin and fluorouracil plus cetuximab in patients with cancer in the oesophagus or gastro-oesophageal junction - a non-randomised phase II trial.
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
DNA	**D**eoxyribo**n**ucleic **a**cid
EGFR	Epidermal Growth Factor Receptor
FDG-PET	Positron Emission Tomography with FluoroDeoxyGlucose
FEV1	Forced Expiratory Volume in 1 second
FEV%	FEV1/VC
NeoRes	**Neo**adjuvant therapy for **Res**ectable Esophageal cancer
ROS	Reactive Oxygen Species
SEER	Surveillance Epidemiology and End Results. Cancer statistics provided by the National Cancer Institute in the USA
SEGCG	Scandinavian Esophageal and Gastric Cancer Group
VEGF	Vascular Endothelial Growth Factor
VC	Vital capacity

1 INTRODUCTION

1.1 EPIDEMIOLOGY

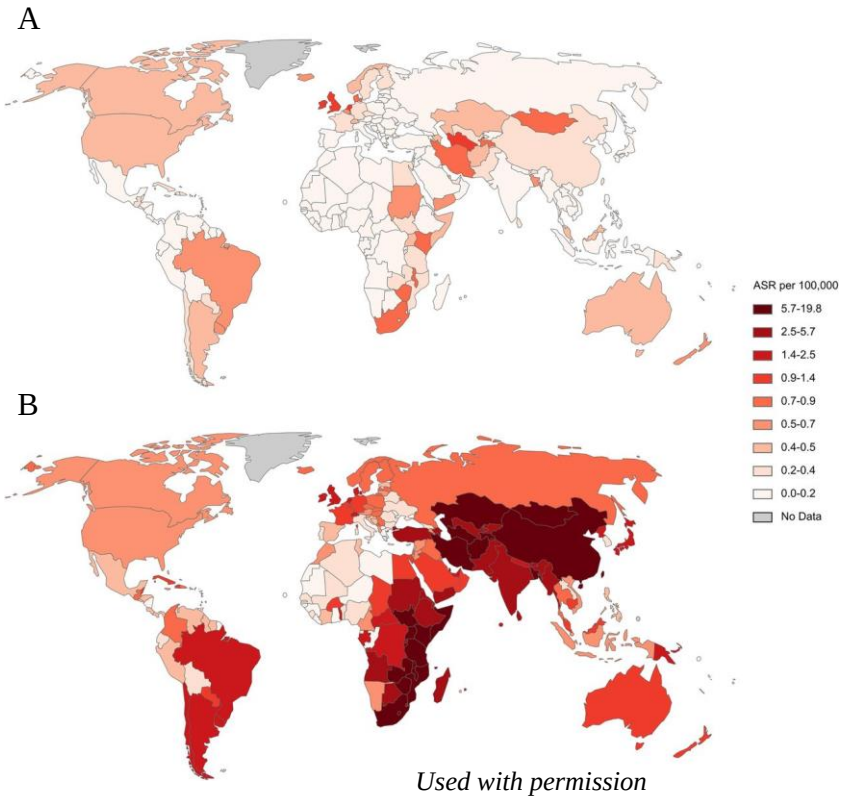
Oesophageal cancer is the twelfth most common cancer worldwide. The prognosis is gloomy visualized by the fact that it is the seventh leading cause of cancer related death[1]. It is a rare disease among the young, and it typically affects people in the seventh and eights decade of life[2].

The vast majority of oesophageal cancers are squamous cell carcinoma or adenocarcinoma. They do not only differ histologically but also with respect to aetiology, geographic distribution and anatomical location.

Adenocarcinoma derives from the glandular cells and typically arises in the lower third of the oesophagus. Squamous cell carcinomas are in most cases located in the upper two thirds of the oesophagus[3].

The geographic distribution is uneven. A high incidence of squamous cell carcinoma is found in South-East and Central Asia and in Southern and Eastern Africa. (Figures 1 and 2). In the western world, oesophageal cancer is still a rare disease, although the incidence of adenocarcinoma is rapidly increasing (Figure 3) and is now the predominant type[4,5]. The incidence of oesophageal cancer in Sweden 2014 was 2.6 per 100 000 women and 8.0 per 100 000 men[6].

Figure 1 *Age-standardized incidence rate (ASR) per 100 000 of (A) oesophageal carcinoma and (B) squamous cell carcinoma in women*



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Melina Arnold *et al. Gut 2015;64:381-387*

Figure 2 *Age-standardised incidence rate (ASR) per 100 000 of (A) oesophageal adenocarcinoma and (B) squamous cell carcinoma in men.*

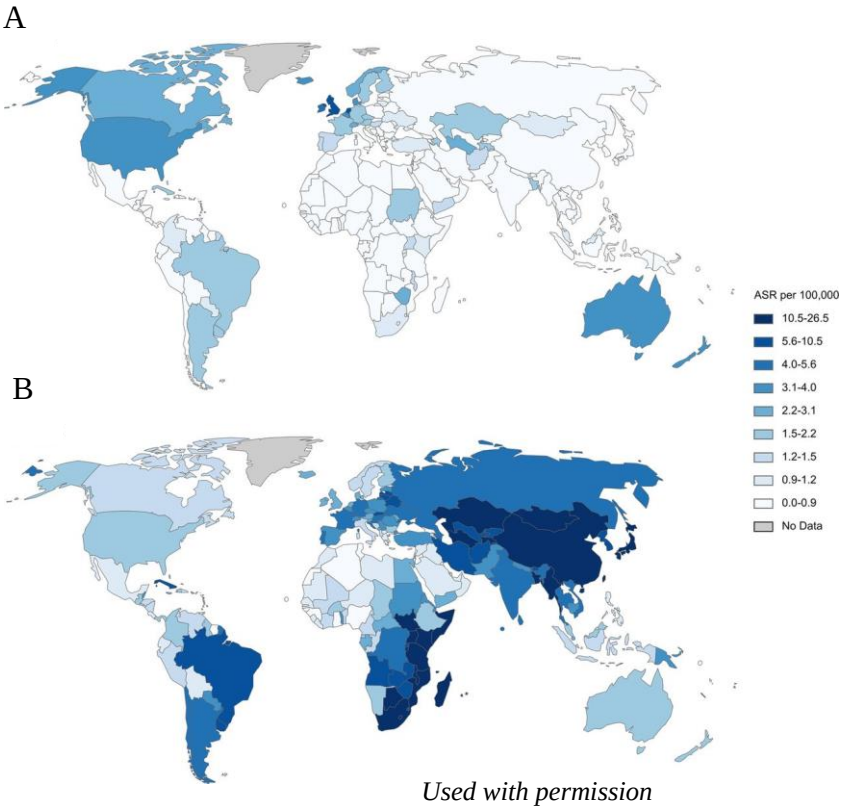

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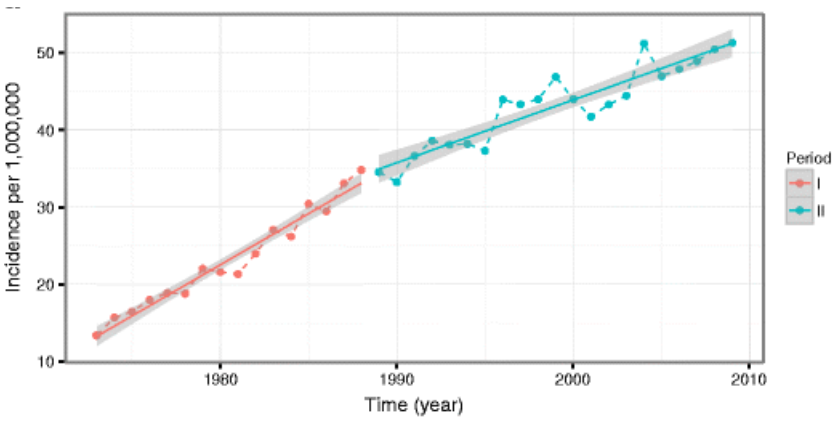
Figure 3 *Incidence of adenocarcinoma of the oesophagus and the gastric cardia from Surveillance Epidemiology and End Results (SEER) 9 database from the National Cancer Institute in the USA.*



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Dubecz A *et al. Journal of Gastrointestinal Surgery 2014; 18(1): 124-9.*

1.2 RISK FACTORS

1.2.1 Smoking

Tobacco smoking multiplies the risk of developing squamous cell carcinoma in the oesophagus. There is also a link between smoking and adenocarcinoma, even though the association is weaker than for squamous cell carcinoma. Several studies have been conducted to investigate the relationship between tobacco use and the development of oesophageal cancer and there seems to be a dose-dependent association between tobacco smoking and the evolution of oesophageal cancer[7]. It has also been shown that in the development of squamous cell carcinoma, tobacco smoking acts synergistically with alcohol consumption[8].

1.2.2 Alcohol

Alcohol intake is a major risk factor for the development of squamous cell carcinoma in the oesophagus and it seems to be due to the metabolite of ethanol, acetaldehyde, that interferes with DNA synthesis and repair[9]. This is also supported by the fact that Asians, who have a deficiency in aldehyde dehydrogenase which causes an accumulation of acetaldehyde, have an increased risk of developing the disease[10]. Similar to tobacco smoking, there seems to be a dose-response relationship between alcohol intake and the development of squamous cell carcinoma of the oesophagus[11]. However, there does not seem to be any relation between the development of adenocarcinoma and alcohol consumption[7].

1.2.3 Gastro-oesophageal reflux and obesity

Gastro-oesophageal reflux disease is a major risk factor for developing adenocarcinoma in the oesophagus[12]. Obesity increases the risk of reflux, but even in the absence of reflux obesity is a risk factor for oesophageal cancer[13].

1.2.4 Barrett´s oesophagus

The squamous cells of the oesophagus can be replaced by metaplastic columnar epithelium as a consequence of chronic exposure to gastric acid and bile. This so-called Barrett´s metaplasia gives no symptoms and is commonly discovered at endoscopic examination of patients with gastro-oesophageal reflux. Patients with Barrett´s oesophagus have an increased risk of developing adenocarcinoma in the oesophagus. In a high-quality meta-analysis patients with Barrett´s oesophagus have been estimated to have an annual risk of developing high-grade dysplasia or adenocarcinoma of approximately 0.77%[14].

1.3 CLINICAL PRESENTATION

Dysphagia is the most common symptom of oesophageal cancer. In a survey of patients with oesophageal cancer in North-America as many as 74% reported dysphagia at diagnosis. Odynophagia were present in 17% and 57% had experienced weight loss. Heartburn was present in 21%[15]. Even though symptoms from gastro-oesophageal reflux are common among patients with oesophageal cancer, it is also common in the general population where the vast majority does not suffer from oesophageal cancer. In a population-based study of mainly white North-Americans, 20% suffered at least on a weekly basis of heartburn and/or acid regurgitation[16].

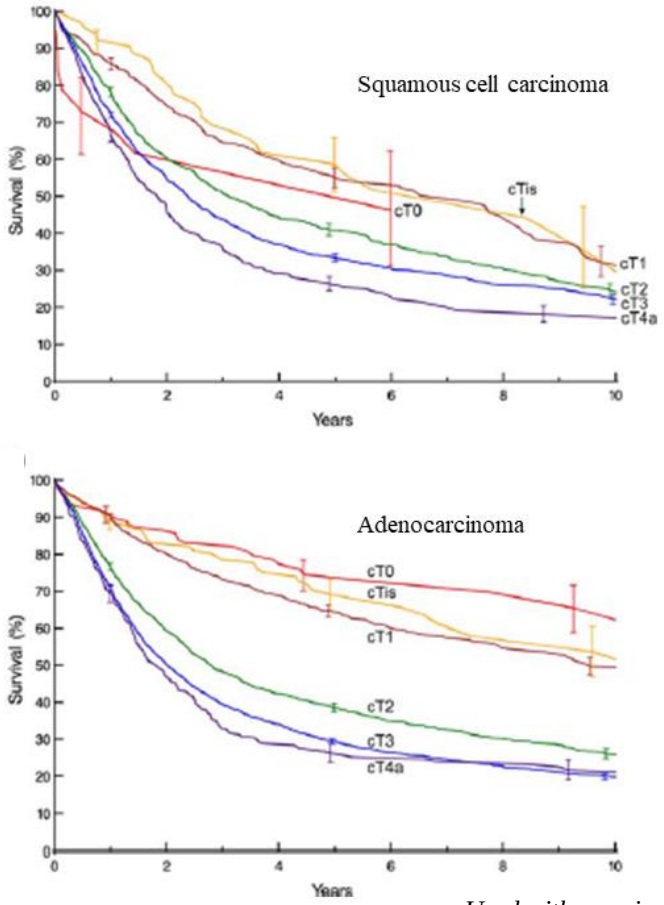
1.4 DIAGNOSIS

Upper endoscopy in general clinical practice is a reliable method to detect oesophageal cancer with a sensitivity as high as 94%[17]. For staging purposes, it is essential to detect lymph nodes and distant metastases. Computed tomography (CT) is easily accessible in most diagnostic centres, but has its limitations in detecting non-enlarged metastatic lymph nodes, differencing between benign and metastatic enlarged lymph nodes and detecting minor distant metastases. Endoscopic ultrasound has a higher detection rate of regional metastatic lymph nodes[18], but is highly dependent on the skills of the examiner[19]. Fluorodeoxyglucose (FDG) positron emission tomography (PET) can measure metabolic activity in the body. When combined with a CT, three-dimensional images can be created and the sensitivity and specificity for detecting distant metastases is better than for CT alone[20].

1.5 STAGING AND PROGNOSIS

Oesophageal cancer is classified in the American Joint Committee on Cancer Tumor-Nodes-Metastasis (TNM) staging system and the latest edition (8th edition) was published in 2016. The classification takes into account the size and invasion of adjacent structures of the primary tumour, the amount and location of lymph node-metastases, the prevalence of distant metastases and histologic grading. In the latest edition there are different grading systems for clinical staging (cTNM), pathologic staging (pTNM) and after neoadjuvant treatment (ypTNM). The prognosis is highly dependent on the TNM staging[21-23] as illustrated by Figure 4.

Figure 4 *Survival by clinical T category. Kaplan–Meier estimates accompanied by vertical bars representing 68% confidence limits, equivalent to ±1 standard error.*



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Rice TW et al. *Diseases of the Esophagus 2016;29(7):707-714*

The overall survival in patients diagnosed with oesophageal cancer is poor, and the 5-year survival rate among those registered in the SEER database in the United States between the years 2001-2009 was 22 %. The poor diagnosis is partly reflected by the fact that as many as 37% have distant metastases at the time of diagnosis.[24]

It is generally accepted that complete tumour regression in the resected specimen after neoadjuvant treatment is a major prognostic factor for patients with oesophageal carcinoma[25]. When there is residual carcinoma, there are several different grading systems for assessing the response of neoadjuvant therapy and thereby predicting outcome. Some of the grading systems exclusively focus on response at the primary site, and some incorporate both nodal and primary site response. The most commonly used grading system in oesophageal cancer is the five-graded scale suggested by Mandard in 1994, which focuses on response in the primary site[26,27]. Chirieac and co-workers modified the Mandard scale to a simpler four-graded scale (Figure 5), similar to the one used in the evaluation of gastric cancer by Becker and co-workers [25,28]. Chirieac found an association between survival and histopathologic grading after neoadjuvant chemoradiotherapy in 235 patients with adenocarcinoma or squamous cell carcinoma in the oesophagus (Figure 6). The scale developed by Chirieac was later used when analysing the specimens in the CROSS trial[29] and was also used in the NeoRes I trial.

Figure 5 *Histopathologic grading of the primary tumour after neoadjuvant treatment as suggested by Chirieac*

(A) No residual carcinoma, characterized by microscopic evidence of radiation-induced tissue injury, regenerative changes, and fibrosis extending through the layers of the oesophageal wall. There is no histologically identifiable residual carcinoma.

(B) 1–10% residual carcinoma, characterized by rare individual carcinoma cells present in fibrotic tissue at the primary site.

(C) 11–50% residual carcinoma, characterized by microscopic foci of carcinoma cells present at the primary site.

(D) Greater than 50% residual carcinoma, characterized by substantial carcinoma remaining at the primary site.

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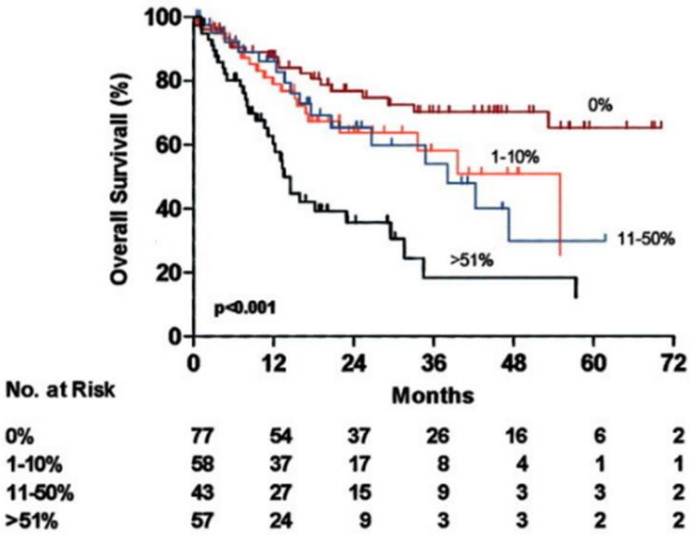
Chirieac LR *et al. Cancer. 2005;103(7):1347-1355.*

Figure 6 *Kaplan–Meier estimates of overall survival among patients with carcinoma of the oesophagus and oesophagogastric junction treated with preoperative neoadjuvant chemoradiation. Grading of residual carcinoma as suggested by Chirieac.*



No. at Risk							
0%	77	54	37	26	16	6	2
1-10%	58	37	17	8	4	1	1
11-50%	43	27	15	9	3	3	2
>51%	57	24	9	3	3	2	2

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Chirieac LR *et al. Cancer. 2005;103(7):1347-1355.*

2 TREATMENT

The choice of treatment for patients with oesophageal cancer depends on a variety of factors such as stage of the disease, location of the tumour, comorbidities and age of the patient. When the tumour has not spread beyond regional lymph nodes it is a potentially curable disease. But, often patients present with advanced (metastatic) disease and cure is out of reach. Curative treatment consists of surgery alone, chemoradiotherapy or a combination of surgery and chemotherapy with or without the addition of radiotherapy.

2.1 CURATIVE TREATMENT

2.1.1 Surgery

Surgery can be performed in different ways when resecting oesophageal cancer. The two stage thoraco-abdominal approach (Ivor Lewis) is the most frequently used for tumours in the lower third of the oesophagus. The three-stage oesophagectomy (McKeown) where there is also a cervical incision is more regularly used in the upper third of the oesophagus. In three-stage oesophagectomy a cervical lymph node dissection (=three-field lymphadenectomy) may or may not be added. Three-field lymphadenectomy is often practiced in Asia for mid and upper third cancers, while practiced much more restrictively in Western countries. Results from ongoing randomised trials in China and India comparing two-field and three-field lymphadenectomy are awaited. A gastric tube, constructed out of the major curvature of the stomach with vascular supply mainly from the right gastroepiploic vessels, is used to substitute the oesophagus and the anastomosis is either intrathoracic or cervical.

A less traumatic procedure is the trans-hiatal approach, which can be used for tumours in the lower half of the oesophagus. As the lymph node dissection then is performed from the abdomen it will not be as radical in the mid and upper part of the mediastinum as it will be with the transthoracic approach.

A randomised study comparing the trans-hiatal and the thoracic-abdominal approach has not shown any survival advantage for either of the two techniques. However, in a sub-group analysis a survival benefit in favour of the thoraco-abdominal approach was shown for those with a limited number of pathological lymph nodes[30]. In clinical practice, nodal staging before surgery is often not consistent with pathological staging. Therefore, the thoraco-abdominal technique is often advocated if the patient is fit enough[31].

In recent years minimal invasive techniques have been introduced. With this procedure endoscopic methods are used instead of thoracotomy and laparotomy. The TIME-trial[32] shows short-term advantages in terms of reduced morbidity and enhanced recovery after surgery without jeopardizing the R0-resection rate and the number of lymph nodes retrieved. The findings are supported by the MIRO-trial presented at ESMO in 2017[33].

2.1.2 Chemotherapy

The role of chemotherapy in the curative treatment of oesophageal cancer is to eliminate micrometastases and downsize the primary tumour. When given concurrent with radiotherapy it enhances injury to the deoxyribonucleic acid (DNA) or prevents its repair with the aim to overcome radioresistance of the tumour[34]. Chemotherapy cannot as a single modality cure oesophageal cancer.

The use of neoadjuvant chemotherapy and chemoradiotherapy developed in the 1970s[34]. The agents chosen were drugs that had been shown to be successful in other tumours. The use of cisplatin-based regimens in a pre-operative setting was first reported from Memorial Sloan-Kettering[35] and the use of cisplatin is still considered the gold standard in the neoadjuvant treatment of oesophageal cancer. The mode of action of cisplatin is cross-linking with the purine bases in the DNA and thereby causing DNA-damage and interference with DNA repair mechanisms, which results in apoptosis[36].

Cisplatin was at first combined with bleomycin that was later replaced by fluorouracil[37] which have fewer pulmonary side effects. Fluorouracil is an antimetabolite which inhibits the action of thymidylate synthase and the replication and repair of DNA is thereby hampered. Fluorouracil is also incorporated into RNA which results in impaired function of RNA[38] and the antitumoural effect is enhanced. Other drugs have been combined with cisplatin, but fluorouracil is probably the most well-documented radio-sensitizer[34] and the combination of fluorouracil and cisplatin is well established in the treatment of oesophageal cancer. The US collaborative group, CALGB, showed that the addition of neoadjuvant cisplatin, fluorouracil and radiotherapy to surgery improved 5-year survival from 16 to 39% compared to surgery alone[39] and Ychou *et al.* found that peri-operative cisplatin- fluorouracil improved 5-year survival for patients with gastro-oesophageal adenocarcinoma compared to surgery alone from 24 to 38%[40]. A newer platinum analogue, oxaliplatin, appears to be as effective as cisplatin in the treatment of oesophageal cancer[41,42], but has a shorter infusion time and fewer ototoxic and renal side effects. Like cisplatin, oxaliplatin reacts with DNA bases which results in DNA cross-links[43].

A more recently developed group of drugs are the taxanes which may provide additional benefit in the neoadjuvant setting. Taxanes disrupt microtubule function in the cells and thereby cell cycle progression is suppressed and apoptosis may be triggered[44]. In Japan, there is an ongoing three-armed trial, NExT, comparing neoadjuvant cisplatin- fluorouracil with or without the addition of radiotherapy and neoadjuvant cisplatin- fluorouracil -taxane in the treatment of squamous cell carcinoma in the oesophagus[45]. The CROSS trial[46], where surgery alone was compared with neoadjuvant weekly carboplatin and taxane concurrent with radiotherapy followed by surgery, has received much attention. In this trial the addition of chemoradiotherapy to surgery improved 5-year survival from 33 to 47%. These promising

results warrant further investigations to compare the effect with other neoadjuvant regimens. There are conflicting results from retrospective analyses comparing the CROSS-regimen with neoadjuvant cisplatin- fluorouracil[47,48] and results from prospective trials are awaited. There are two ongoing trials, Neo-AEGIS and ESOPEC, comparing the CROSS regimen with the MAGIC regimen (peri-operative epirubicin, fluorouracil and cisplatin) or the FLOT-regimen (peri-operative fluorouracil, folinic acid, oxaliplatin and docetaxel) in patients with adenocarcinoma in the oesophagus or oesophago-gastric junction. There is also an ongoing trial in France, PROTECT, comparing the CROSS regimen with neoadjuvant oxaliplatin, fluorouracil and folinic acid (FOLFOX) concurrent with radiotherapy in patients with resectable cancer in the oesophagus or oesophago-gastric junction.

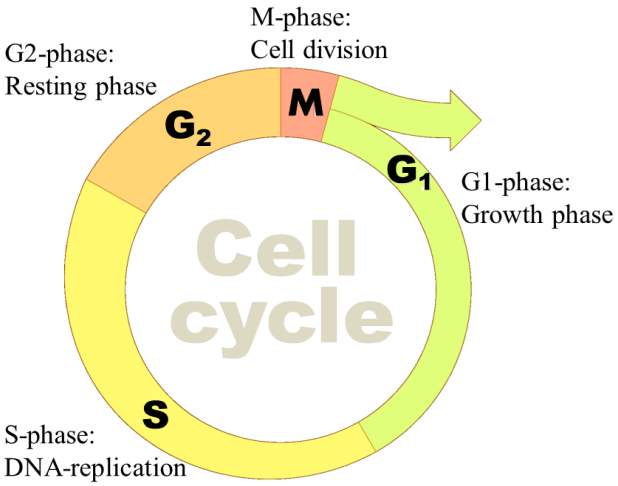
2.1.3 Radiotherapy

Radiotherapy in combination with chemotherapy with[46] or without surgery[49] can cure oesophageal cancer. However, radiotherapy used as a single modality is not an option when there is a curative intent. In the landmark trial conducted in the 1980s, RTOG 85-01, patients with oesophageal cancer were randomised to receive 64 Gy of radiotherapy or 50 Gy of radiotherapy concurrent with cisplatin and fluorouracil. Five-year survival was 26% among those randomised to receive chemoradiotherapy whereas none of the 62 patients randomised to receive radiotherapy were alive after 3 years[49].

When there is a curative intent, radiotherapy is given in small fractions during a couple of weeks, so called fractionated radiotherapy. The mechanisms that determine the response of tumours and normal tissues to fractionated radiotherapy are often referred to as the 4 R´s of radiobiology: **R**epair of DNA damage, **R**edistribution of cells in the cell cycle, **R**epopulation, and **R**eoxygenation of hypoxic tumour areas:

Repair of DNA: Radiotherapy generates highly reactive free radicals from water molecules, so called reactive oxygen species (ROS). The ROS cause lethal and sublethal damage to the DNA. Malignant cells often have suppressed repair pathways preventing them from sufficient repair before the next dose of radiation is given during a course of fractionated radiotherapy[50]. Normal cells however will be able to repair the sublethal damage between radiotherapy doses. Chemotherapy may enhance the effect of radiotherapy through inhibition of the repair process of sublethal damage.

Figure 7 *Phases of the cell cycle*



Source: *Personal collection*

Redistribution of cells in the cell cycle: Cells exhibit different radiosensitivity during different phases of the cell cycle which was shown already in 1968[51]. The phases of the cell cycle are visualized in Figure 7.

During the relatively brief period of the cell cycle when the chromosomes are separated, the mitotic phase (M-phase), the cells are most sensitive to DNA-damaging agents. In opposite, in the late S-phase when the replication of the DNA is finished the cells are most resistant to

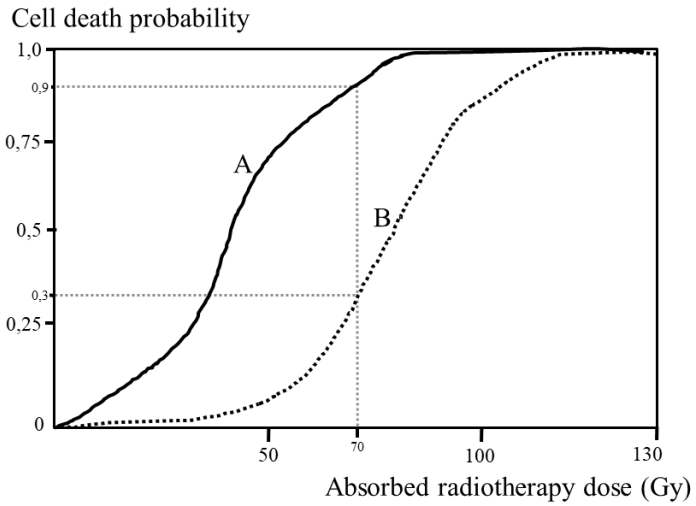
radiation. Chemotherapeutic agents may enhance the effect of radiotherapy through redistributing cells to the more radiosensitive parts of the cell cycle.

Repopulation: During the later phase of a radiotherapy course the tumour can speed up the regeneration of new tumour cells[52]. This so called accelerated repopulation can be inhibited by cytotoxic agents.

Reoxygenation: Solid tumours have smaller or larger volumes that are less well oxygenated than normal tissues. The resulting hypoxia may inhibit but it may also accelerate tumour progression. Inhibition is caused by cell-cycle arrest, apoptosis and necrosis of tumour cells. Accelerated progression may be promoted by hypoxia through evolution of mechanisms that enable tumour cells to overcome nutritive and oxygen deprivation[53]. Hypoxia also increases the resistance to radiotherapy and chemotherapy[54]. During the course of fractionated radiotherapy, the proportion of hypoxic cells remain constant which is a proof of hypoxic cells becoming reoxygenated[55]. This phenomenon where hypoxic cells become oxygenated during fractionated radiotherapy is called reoxygenation.

The rationale behind giving fractionated radiotherapy is to allow the *repair* of normal tissues from sublethal damage and *repopulation* of normal cells between treatments. At the same time tumour cells are *reoxygenated* and *redistributed* into more radiosensitive parts of the cell cycle and the likelihood of tumour control increases. Tumour cells have less capacity to recover than normal cells, and the aim of radiotherapy is to deliver enough radiation to kill the tumour cells but not so much radiation that seriously damage normal tissues. This can be illustrated by a schematic dose-response curve as shown in Figure 8. In this example the probability of tumour control is 90 % and the probability of normal tissue complications is 30% when the absorbed radiotherapy dose is 70 Gy.

Figure 8 *Dose-response curve*
Curve A shows the probability of tumor control.
Curve B shows the probability of normal tissue complications



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It has not been established what the optimal radiotherapy dose is in the preoperative setting for oesophageal cancer. In randomised studies comparing surgery alone and neoadjuvant chemoradiotherapy followed by surgery doses from 20 to 50.4 Gy have been used[56]. In a meta-analysis there seems to be a dose-response relationship[57]. However, the optimal radiotherapy dose depends on selection and dose of drugs given concurrent with radiotherapy as well as age and comorbidity of the patient.

When delivering definitive chemoradiotherapy the gold standard is 50 Gy. In 2002, data from a randomised trial comparing high dose (64.8 Gy) to standard dose (50.4 Gy) concurrent with chemotherapy was published[58]. Dose escalation could not be proven to increase survival or loco-regional control. However, the radiotherapy techniques have evolved since then, and there are ongoing trials (for example the French Concorde trial, the Dutch Art-Deco trial and the British SCOPE 2 trial) addressing the question whether radiotherapy dose escalation will improve prognosis.

Whether or not to include elective lymph nodes in the radiation field is a matter of controversy. Oesophageal cancer is well known for its tendency for early lymphatic spread and the idea is theoretically attractive. However, there is no strong evidence to support this view[59]. There are retrospective data suggesting that elective lymph node irradiation when given as definitive chemoradiotherapy[60] or as a preoperative treatment[61] reduces the risk of regional lymphatic recurrence or at least delays the recurrence but there is no gain in survival. Modern radiotherapy techniques such as Intensity Modulated Radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) will deliver more conformal treatment than previously used techniques. Consequently, previously incidentally irradiated lymph nodes will with the new techniques not be irradiated and recurrence patterns need to be followed carefully.

2.1.4 Neoadjuvant treatment

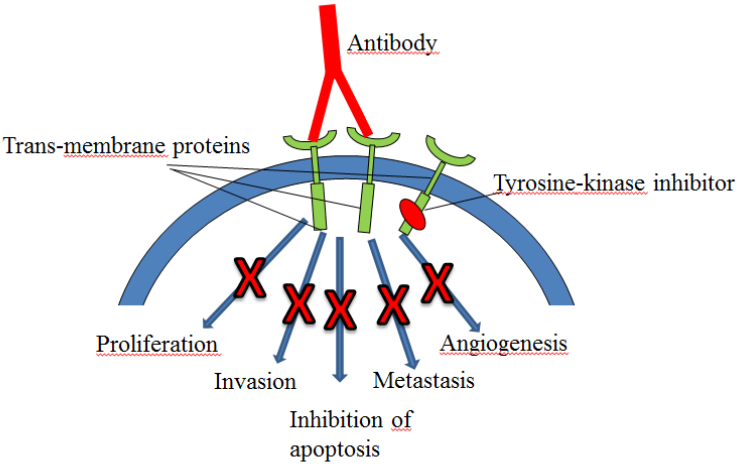
Several randomised controlled trials have compared different chemotherapy or chemoradiotherapy regimens combined with surgery versus surgery alone in patients with oesophageal cancer. Meta-analyses from the Australasian Gastro-Intestinal Trials Group and from the Cochrane library have shown a clear survival benefit for multimodality treatment to surgery alone[56,62]. The survival advantages were seen in both squamous cell carcinoma and adenocarcinoma, although it did not reach statistical significance in patients with squamous cell carcinoma treated with neoadjuvant chemotherapy. The treatment effect did not seem to be as large for neoadjuvant chemotherapy as for neoadjuvant chemoradiotherapy and an indirect comparison showed a trend towards survival benefits for neoadjuvant chemoradiotherapy compared to neoadjuvant chemotherapy. Direct comparisons provide a higher level of evidence than indirect comparisons, and prior to the publication of the NeoRes I trial there have been only two randomised clinical trials comparing the effect of neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy in the treatment of oesophageal adenocarcinoma. Stahl *et al.* evaluated 119 patients with adenocarcinoma in the distal oesophagus or gastric-oesophageal junction (Siewert I-III) who had been randomly assigned to receive neoadjuvant treatment with 14.5 weeks of cisplatin, fluorouracil and leukovorin or 12 weeks of cisplatin, fluorouracil and leukovorin followed by three weeks of cisplatin and etoposide given concurrently with radiotherapy (2 Gy x 15)[63,64]. Burmeister *et al.* randomised 75 patients with adenocarcinoma in the oesophagus or gastric-oesophageal junction to receive neoadjuvant treatment with 6 weeks of cisplatin and fluorouracil with or without the addition of radiotherapy (3 Gy x 15)[65]. In both trials there were significantly better pathologic response rates among those who received radiotherapy in addition to chemotherapy. This was however not translated into better overall survival, although there was a trend towards better survival in favour of chemoradiotherapy in the trial conducted by Stahl *et al.* No corresponding comparative trials with modern surgical techniques have been completed in patients with squamous cell carcinoma.

2.1.5 Targeted therapies

With increasing insights into the molecular pathways of carcinogenesis, a variety of molecular targeted agents have been developed. These drugs interfere with signaling pathways that in various ways regulate cell growth and proliferation. Also in oesophageal cancer there are several pathways involved in the carcinogenesis that are potential targets for drugs.

The human epidermal growth factor receptor (EGFR) is a trans-membrane protein. When activated it causes activation of intracellular pro-oncogenic pathways. Several drugs have been developed to block the extracellular domain, such as the anti-EGFR antibodies cetuximab and panitumumab. Other smaller drugs, tyrosine-kinase inhibitors such as gefitinib and erlotinib, have been developed to pass the cellular membrane and block the intracellular portion of the protein (Figure 9).

Figure 9 *Cellmembrane with transmembrane proteins. Blockage of the transmembrane proteins (eg EGFR) with an antibody or a tyrosine-kinase inhibitor will inhibit intracellular signals and thereby inhibit carcinogenesis.*



Source: *Personal collection*

High expression of the transmembrane protein EGFR has been shown to be a negative prognostic factor in patients with adenocarcinoma or squamous cell carcinoma in the oesophagus[66,67]. When activated, EGFR causes activation of intracellular pro-oncogenic pathways. This is the rationale behind targeting the EGFR-pathway in the treatment of oesophageal cancer.

In 2008 data were published showing promising results for cetuximab in addition to chemoradiotherapy in the treatment of patients with oesophageal cancer[68]. A few years later, in 2013, Crosby *et al*. published discouraging results from a randomised trial where cisplatin, capecitabine and radiotherapy were given with or without cetuximab. They found that treatment intensity was decreased in patients receiving cetuximab compared to those only receiving chemoradiotherapy. In the long-term follow-up, there was no significant difference in overall survival between those allocated to receive cetuximab and those allocated to chemoradiotherapy alone, but survival was decreased in patients who received lower doses of chemotherapy and radiotherapy[69,70]. Soon after the initial report from Crosby and co-workers, Suntharalingam *et al.* presented data showing that when adding cetuximab to cisplatin, paclitaxel and radiotherapy overall survival did not increase[71]. Disappointingly, nor have any of the other drugs targeting the EGFR-receptor showed any benefits for patients with oesophageal cancer.

Another transmembrane protein is the ErbB2, frequently called HER-2. When activated, downstream oncogenic pathways are triggered. Several drugs have been developed to target the pathway and the antibody trastuzumab directed against the extracellular domain has been proven to be efficient in metastatic HER-2 overexpressing adenocarcinomas arising from the gastro-oesophageal junction[72].

Vascular endothelial growth factor, VEGF, is a family of transmembrane proteins involved in angiogenesis which is essential for tumour growth. Ramucirumab, an antibody directed against the VEGF 2, has a modest activity in the treatment of advanced cancers deriving from the gastro-oesophageal junction[73,74].

2.2 SIDE EFFECTS

One of the central tenets of medical ethics is to do no harm. This forms an ethical dilemma to surgeons and oncologists treating patients with oesophageal cancer as treatment with curative intent is highly toxic. When using evidence-based medicine physicians prescribe treatment that is more likely to benefit than to harm the patient. Still, in many types of cancer with high mortality rates such as oesophageal cancer, a number of patients are given toxic treatments they derive little benefit from. When assessing the risks versus benefits of different treatment options for a given patient, physicians need a thorough understanding of both the risks and the benefits of the available treatment options. The benefits of treatments are often well documented, however, toxicity data from treatment of oesophageal cancer are more scarcely reported, especially long-term toxicity[75].

2.2.1 Side effects from chemotherapy

The toxicity of chemotherapy used in the treatment of oesophageal cancer is similar to the toxicity from treatment of other cancers. Chemotherapy causes more or less invariably some level of acute bone marrow depression. Depending on the severity of the depression this may result in serious infections, sometimes even life-threatening. More infrequently thrombocytopenia results in bleeding complications. Nausea and vomiting are common acute side effects of chemotherapy that in complicated cases and/or if not adequately treated may result in decreased treatment intensity. Some chemotherapeutic agents may cause acute allergic reactions. Depending on the choice of chemotherapy acute and long-term ototoxic, renal and neurotoxic effects are also seen.

2.2.1.1 Cardiac side effects from chemotherapy

Fluorouracil is one of the most widely investigated antineoplastic agents in respect of causing myocardial ischemia[76]. Silent ischemic changes have been found in as many as 68% of patients receiving continuous fluorouracil. Changes in the electrocardiogram (ECG) were more frequent among patients who had known coronary artery disease[77]. Cardiac arrhythmias has also been reported in conjunction with fluorouracil infusion[78]. Typically the cardiac side effects arise during the infusion, and stops after cessation of the treatment[76]. The mechanisms behind the cardiotoxic effects of fluorouracil are not fully understood, but vasospasm has been suggested to be a main contributor. Other potential contributors are endothelial dysfunction causing thrombosis and direct myocardial injury[79].

Cisplatin has also been implicated as a cause of arrhythmias and ischemic cardiac disease[76], even though not as well investigated as fluorouracil. The mechanisms behind have been suggested to include vascular damage, dysfunction in the platelet aggregation and hypomagnesemia[80].

2.2.1.2 Pulmonary side effects from chemotherapy

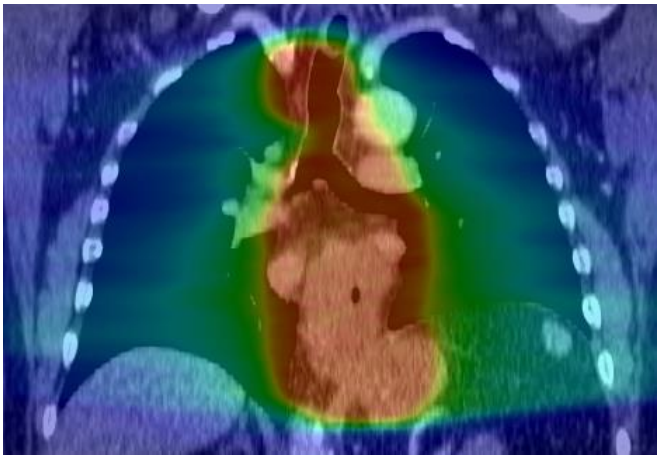
Pulmonary toxicity is a well-known side effect of some chemotherapeutic agents. In the acute setting interstitial pneumonitis characterized by progressive dyspnoea and sometimes fever might be observed. The most common late onset toxicity is pulmonary fibrosis manifesting itself by dyspnoea, non-productive cough and fever. One of the most well-known agents to cause pulmonary toxicity is bleomycin, a drug that has been used since the 1960s. However, agents commonly used in the treatment of oesophageal cancer rarely exert pulmonary toxic effects. Although, oxaliplatin[81] and taxanes[82] have both been described to cause interstitial pneumonitis. In a study of 86 patients with breast cancer or lymphoma treated with radiotherapy, with or without the addition of chemotherapy, an acute reduction of pulmonary function tests was seen after treatment. Chemotherapy was seen to aggravate the reduction

caused by radiotherapy[83]. In the long-term follow up, the additive effect of chemotherapy to radiotherapy was however abolished[84].

2.2.2 Side effects from radiotherapy

When administering radiotherapy, nearby organs to the target will be incidentally irradiated as illustrated by the dose distribution in Figure 10. Therefore, common side effects from radiotherapy of the oesophagus are related to irradiation of the oesophagus, the heart and the lungs. The extent of side effects is related to the radiation dose and to the irradiated volume.

Figure 10 *Example of radiation therapy dose distribution from treatment of oesophageal cancer. High dose is coloured red and low dose is blue. The heart and the lungs are just next to the oesophageal tumour.*



Source: *Personal collection*

2.2.2.1 Oesophageal side effects from radiotherapy

Mucosal cells lining the oesophagus have a rapid turnover and acute side effects from the oesophagus are more or less invariably seen when treating oesophageal cancer with radiotherapy. Acute oesophagitis can, depending on individual radiosensitivity and radiation doses, be severe and cause grave dysphagia. Late oesophageal side effects from radiotherapy include strictures, chronic ulcers and fistulas. Patho-morphologically fibrosis is seen.[85]

2.2.2.2 Cardiac side effects from radiotherapy

Ever since the 1960s when radiotherapy of Hodgkin´s lymphoma had become more frequent it has been known that the heart might be damaged by radiotherapy. The risk increases with radiotherapy dose and other risk factors for cardiovascular disease[86]. Much of the knowledge of radiation-induced cardiac disease derives from studies of patients with Hodgkin´s lymphoma or breast cancer as these patients often are long-term survivors of cancer. Due to a relatively low incidence and low cure rates, data on cardiac morbidity after treatment for oesophageal cancer is scarce. However, better treatment strategies have resulted in better long-term outcome, and cardiac morbidity in patients treated for oesophageal cancer is therefore becoming a concern.

Acute radiation-induced pericarditis usually appears within a few weeks after cessation of radiotherapy manifesting itself by fever, tachycardia and chest pain. It is usually self-limiting, but approximately 20% later develop chronic pericarditis[87], which can be asymptomatic or it can be severe with risk of tamponade[86]. Chronic pericarditis may also develop without previous signs of acute pericarditis[88]

Radiation also causes vascular damage. After irradiation there is an increased vascular permeability followed by inflammatory infiltrate. This results in collagen disposition and fibrosis eventually resulting in coronary artery disease which typically is clinically manifested 10-15 years after exposure as ischemic heart disease[87].

Various disturbances in the conduction system have been described such as sick sinus syndrome, various degrees of atrio-ventricular blocks and ventricular arrhythmias[88].

The myocardial cells divide slowly and are relatively resistant to radiotherapy, but interstitial fibrosis may occur[89] as a result of vascular leakage. This in turn may lead to systolic and diastolic dysfunction[90].

There is also an increased risk of valvular disease after thoracic irradiation although the latency period is very long. In a retrospective study of patients with Hodgkin´s lymphoma the median time to symptoms was 22 years[91].

2.2.2.3 Pulmonary side effects of radiotherapy

Pulmonary side effects from radiotherapy after treatment of Hodgkin´s lymphoma, breast cancer and lung cancer are fairly well documented, but the effects on patients treated for oesophageal cancer are scarcely reported.

Acute pulmonary reaction after radiotherapy, pneumonitis, is usually manifested within 1-3 months after treatment with cough, dyspnoea and fever. The histopathologic findings are characterized by injury to small vessels and oedema[92] which pathologists reported already in 1939[93].

Late pulmonary side effects after radiotherapy are characterized by fibrosis, which is a chronic pulmonary damage. Patients with acute pneumonitis may later develop fibrosis, but it may also develop without a previous history of pneumonitis. Patients with radiographic findings of fibrosis may have no symptoms from the lungs, or they may have varying degrees of dyspnoea which sometimes can be very disabling[92].

In patients treated for breast cancer or lymphoma with radiotherapy with or without the addition of chemotherapy, pulmonary function tests have been found to be decreased in the acute setting and in the long-term follow-up[84,94,95]

The cardiopulmonary side effects caused by radiotherapy might be reduced when using newer radiotherapy techniques. There are data suggesting that the use of IMRT could reduce post-operative pulmonary complications after oesophageal resection by reducing mean-lung dose[96]. A recently published retrospective trial found a lower rate of cardiac mortality among patients with oesophageal cancer older than 65 years treated with IMRT than for those treated with 3D conformal radiotherapy[97] which might suggest that sparing of the heart and/or lungs results in lower cardiac mortality. However, with the use of IMRT, or the more recently developed technique VMAT, larger volumes of the lungs will receive low doses of radiation and the clinical effects of this remain to be established.

2.2.3 Measurement of pulmonary function

The most frequently used test of pulmonary function is the spirometry[98] when exhaled volumes of air are measured. Such volumes are the vital capacity (VC), which is the maximum volume of air that can be exhaled after full inspiration, and the forced vital capacity in one second (FEV1), which is the maximum amount of air that can be exhaled during the first second after full inspiration. The measurement of the diffusion capacity of carbon monoxide (DLCO) gives information on the function of the alveolar membranes and is a more sensitive method to detect drug-induced pulmonary damage[99].

3 AIMS

The aims of this thesis are:

To evaluate if the addition of neoadjuvant radiotherapy to neoadjuvant chemotherapy improves outcome in patients with cancer in the oesophagus or cardia.

To evaluate patterns of recurrence after multimodality treatment with curative intent of cancer in the oesophagus or cardia.

To evaluate the effects on pulmonary function and cardiac exercise tests from multimodality treatment of cancer in the oesophagus or cardia.

To evaluate the efficacy of cetuximab in addition to oxaliplatin, fluorouracil and radiotherapy in the treatment of patients with cancer in the oesophagus or cardia without distant metastasis.

4 MATERIALS AND METHODS

4.1 THE NEORES I TRIAL

Paper I, II and III are reports from the NeoRes I (**Neo**adjuvant therapy for **Res**ectable Esophageal cancer) trial. The trial was conducted by the Scandinavian Esophageal and Gastric Cancer Group, SEGCG, enrolling patients in Sweden and Norway between 2006-2013. Registration number in ClinicalTrials.gov: NCT01362127. No commercial support was given to this study.

4.1.1 Eligibility criteria

Patients with histologically proven adenocarcinoma or squamous cell carcinoma of the oesophagus or oesophagogastric junction with the clinical stages T1N1 or T2-3N0-1 and M0-M1a according to the American Joint Committee on Cancer tumour-nodes-metastasis staging system 6th edition were eligible for inclusion. Patients with cervical cancer were required to be resectable without laryngectomy. Eligible patients were ≤ 75 years, had an Eastern Cooperative Oncology Group performance status of 0 to 1, were free from uncontrolled cardiac disease without a myocardial infarction within 12 months, had no complications from diabetes and no concurrent malignancy within the last five years. All had haematological and renal function within normal limits. A CT of the thorax and abdomen within one month from randomisation was required. Pre-treatment PET and endoscopic ultrasound were optional.

In paper III patients randomised in Trondheim and Stockholm were included in the analysis.

4.1.2 Chemotherapy

All patients were scheduled for three 3-weekly cycles of cisplatin 100 mg/m^2 day 1 and fluorouracil 750 mg/m^2/24 hours, days 1-5. In case of hearing impairment, tinnitus or renal dysfunction cisplatin was replaced by carboplatin (AUC 5) in patients with squamous cell carcinoma or oxaliplatin 130 mg/m^2 in patients with adenocarcinoma. Dose adaptations in case of haematological toxicity were predefined in the study protocol. In case of leukocyte count below 2.5 x10^9/l or thrombocyte count below 75x10^9/l chemotherapy had to be delayed.

4.1.3 Radiotherapy

Patients randomised to receive chemoradiotherapy were planned to receive 40 Gy concomitant with chemotherapy cycle 2 and 3 (2 Gy once daily in 20 fractions, 5 days a week) with a photon beam linear accelerator. A three-dimensional dose planning system was used. For tumours located mainly above the carina, the caudal border of the clinical target volume (CTV) was 5 cm below the tumour and the supraclavicular nodes defined the upper border. For tumours located mainly below the carina, the cranial border of the CTV was 5 cm cranial of the tumour and the lower border was defined by the celiac lymph nodes. In the lateral, anterior, and posterior directions, the CTV should embrace the gross tumour volume and paraoesophageal area with a margin of 1 cm, but also respecting anatomical barriers such as pleura, pericardium, and bone. The planning target volume was according to local routines. The dose to the lungs exceeding 20 Gy was kept as low as possible and was not to exceed one third of the lung volume. The volume of the heart that received >30 Gy was kept to a minimum. The dose to both kidneys was not to exceed 12 Gy, and the dose to one kidney was not to exceed 20 Gy. Maximum dose to the spinal cord was 40 Gy.

4.1.4 Surgery

Surgery was scheduled 4-6 weeks after completion of the neoadjuvant treatment. The recommended operation for cancers in the cardia and in the distal third of the oesophagus was a thoracoabdominal Ivor-Lewis resection with an intrathoracic anastomosis, whereas a three-stage-resection was recommended for cancers in the middle and upper part of the oesophagus. Two field lymphadenectomy was strived for. If the individual surgeon considered it appropriate other procedures were accepted, such as transhiatal oesophagectomy with laparotomy and cervical incision for distal or junctional cancers, or total gastrectomy for junctional tumours classified as Siewert II.

4.1.5 Assessments during treatment

Patients were reviewed every third week before administration of chemotherapy. During treatment with radiotherapy patients were assessed once weekly. Symptoms were assessed with the US National Cancer Institute´s Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

4.1.6 Follow-up

Follow up visits with clinical assessment were planned every third months during the first two years, and then every sixth months until five years after the end of treatment. Radiographic evaluation and endoscopy were performed on suspicion of recurrent disease.

4.1.7 Histopathological evaluation

All surgical specimens were analysed at Karolinska University Hospital in Stockholm by a single pathologist who was blinded to given treatment. Tumour response was classified according to Chireac *et al.*[25] as described in section 1.5. Radical resection was defined as the absence of tumour cells within one mm of any resection margin[100].

4.1.8 Spirometry and cardiac stress tests

Patients were scheduled to perform a spirometry and a cardiac stress test before and after oncological treatment. The investigations after oncological treatment were in most cases carried out 1 to 2 weeks before surgery. According to local routines in Stockholm, a spirometry and a cardiac stress test were done one to two years later, provided the cancer had not recurred. The timespan for the follow-up investigations was wide because of patients' requests and surgical complications.

Cardiac stress tests were performed on a stationary bicycle. Maximum exercise capacity, peak heart rate, peak blood pressure, significant changes on the ST-segment, and significant arrhythmias were recorded. A significant change on the ST-segment was defined as an elevation or depression of more than 1 mm. Significant arrhythmias were defined as atrial fibrillation or frequent ventricular extra beats. Maximum exercise capacity was achieved when the patient reached the subjective maximum exertion level, experienced chest pain, had changes in the electrocardiogram indicating ischemia, had severe arrhythmias or a pathologic blood pressure. In Trondheim, the resistance started at 50 W and was increased by 25 W every 2 minutes. In Stockholm, the resistance was determined individually based on the expected exercise capacity.

Pulmonary function tests were performed with spirometries and carried out under standardized conditions in several different units. The best results of at least 2 consecutive investigations were recorded. Forced expiratory volume in 1 second (FEV1) and vital capacity (VC) were measured and the ratio FEV1/VC (FEV%) was calculated.

4.1.9 Study design and statistics

The NeoRes I trial is a prospective, randomised, multicentre phase II study. Randomisation was performed at the Regional Oncological Centre in Stockholm with a computerized software. At randomisation, patients were stratified on histology. The allocation sequence was concealed to all investigators. All patient data were centrally collected and stored at Karolinska University Hospital and in a web-based database accessible to investigators.

Statistical analyses were performed using the IBM SPSS computer program, version 23 and 24 and Stata software, version 13.1 and 14.0.

4.1.9.1 Paper I and II

The trial required randomisation of 172 eligible patients to have a statistical power to detect an improvement of 15 % in complete histological response in the primary tumour with the use of a two-sided test with 0.80 statistical power and a significance level of 0.05. To compensate for ineligibility, the target number was set to 180 patients. Progression-free survival, overall survival and recurrence patterns were evaluated as secondary endpoints. The time-to-event was estimated with the Kaplan Meier method with the log-rank test to ascertain significance. Progression-free survival was defined as the time from registration until progression or death from any cause. Overall survival was defined as the time from registration until death. Living patients were censored at 60 months after randomisation. Data were analysed according to an intention-to-treat principle. We used cox proportional hazard models for univariate and multivariate analysis of factors with potential prognostic relevance for survival. Binominal logistic regression was used to ascertain effects of baseline characteristics on patterns of recurrence. Associations between categorical variables were tested with Fischer´s exact test and Chi-square test for association. The differences were considered significant at the 5% level ($p < 0.05$).

4.1.9.2 Paper III

A cohort of patients included in the NeoRes I trial, all randomised in Stockholm or Trondheim, were included. Parameters measured after oncological treatment and one to two years later were compared with baseline parameters by using Wilcoxon signed-rank test. For these three time points, changes over time were analysed with Friedman 2-way analysis of variance by ranks test. Mann Whitney U tests were used for detecting the differences between the treatment groups (chemoradiotherapy versus chemotherapy). The possible correlations between parameters were investigated by using Spearman rank correlation test. A p-value < 0.05 was considered statistically significant.

4.1.10 Ethical considerations

The NeoRes I trial was approved by the Research Ethics Committees in Sweden (registration numbers 2006/738-32 and 2008-40332) and Norway (Helseregion Midt-Norge registration number 4.2008.416). All participating patients provided written informed consent.

4.2 THE LERFOX-C TRIAL

Paper IV is the report from the LERFOX-C trial conducted by the Scandinavian Esophageal and Gastric Cancer group, SEGC. Patients were enrolled in Sweden, Denmark and Norway between 2011 and 2014. Registration number in ClinicalTrials.gov is NCT02636088 and EudraCT Number (EU clinical trials register) is 2008-006802-40. Merck Serono contributed with an unrestricted grant and has not been involved in study design, analysis and interpretation of results or writing of the report.

4.2.1 Eligibility criteria

Patients had to be 18-75 years old, have a WHO performance status of 0-2, have an untreated histologically proven adenocarcinoma or squamous cell carcinoma of the oesophagus or oesophagogastric junction (type I and II according to Siewert´s classification[101]) with the clinical stages T2-T4, N0-N3, M0 according to the American Joint Committee on Cancer tumour-nodes-metastasis staging system 7th edition. Patients had non-resectable tumours or were considered non-operable for medical reasons. A CT of the thorax and abdomen was required, an endoscopic ultrasound of the oesophagus was recommended and an FDG-PET was optional. Further eligibility criteria were normal bone marrow, liver and renal function tests. Exclusion criteria included serious concomitant disorders and previous malignancy during the last two years before inclusion.

4.2.2 Chemotherapy

Patients were scheduled for three 3-weekly cycles of fluorouracil 750 mg/m^2/24 hours, days 1-5 and oxaliplatin day 1. Oxaliplatin was given with 130 mg/m^2 in the first cycle. In cycle 2 and 3, that was administered concomitant with radiotherapy, the dose was reduced to 85 mg/m^2. Dose adaptations in case of toxicity were predefined in the study protocol. If the patient experienced gastro-intestinal toxicity, the next chemotherapy cycle was delayed until recovery and in case of CTCAE grade III-IV fluorouracil was reduced by 20% in the following chemotherapy cycles. If the neutrophil count did not recover above 1.0 x 10^9/l before the next chemotherapy cycle was to be given, chemotherapy was to be delayed and granulocyte-colony stimulating factors (G-CSF) was to be given after the following chemotherapy cycle. Dose escalation was not permitted.

4.2.3 Radiotherapy

Concomitant with chemotherapy 50 Gy was given (2 Gy once daily in 25 fractions, 5 days a week) with a photon beam linear accelerator. A three-dimensional dose planning system was used. The boost clinical target volume (CTV)$_{50Gy}$ was to embrace in the lateral, anterior and posterior directions the gross tumour volume (GTV) with a margin of 1 cm, although respecting anatomical barriers such as pleura, pericardium and bone. Cranially and caudally a margin of 20 mm to GTV was recommended. For tumours located mainly above the carina the caudal border of the CTV$_{46\ Gy}$ was recommended to include additional 3 cm caudally of CTV$_{50\ Gy}$ and the supraclavicular nodes defined the upper border. For tumours located mainly below the carina, the cranial border of the CTV$_{46\ Gy}$ was 3 cm cranial of the CTV$_{50\ Gy}$ and the lower border was defined by the coeliac lymph nodes. The planning target volume was according to local routines. Maximum tolerated dose to the spinal canal was 45 Gy, dose to the lungs were not to exceed 20 Gy to 30 % of the volume, dose to the heart were not to exceed 40 Gy to 50% of the volume and dose to the kidneys were not to exceed 17 Gy to 50% of the volume.

4.2.4 Cetuximab

A loading dose of 400 mg/m^2 was given one week before the start of radiotherapy, and thereafter 250 mg/m^2 was given weekly during the course of radiotherapy. To prevent allergic reactions an antihistamine and betametasone was to be given sixty minutes before infusion. Cetuximab was given at least one hour before infusion of oxaliplatin and radiotherapy. Dose adaptations in case of toxicity were predefined in the study protocol. In the case of hypersensitivity grade I or II according to CTCAE, infusion time was to be delayed. If grade III or IV occurred, further cetuximab was not to be given. Administration of systemic anti-neoplastic drugs other than oxaliplatin, fluorouracil and cetuximab resulted in the patient´s removal from the trial.

4.2.5 Assessments during treatment

Patients were reviewed before start of the second chemotherapy cycle and then once weekly during radiotherapy. Symptoms were assessed with the US National Cancer Institute´s Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

4.2.6 Follow-up

Follow up visit with a clinical assessment and a CT-scan were planned four weeks after the end of treatment, and then every sixth months until 36 months after registration. An optional FDG-PET was planned after 12 months.

4.2.7 Study design and statistical analysis

LERFOX-C is a prospective, non-randomised, multicentre phase II study. All patient data were centrally collected and stored in a locked room and in a database accessible to a data-manager at Karolinska University Hospital. The treatment was to be considered promising if the loco-regional control rate at one year was at least 50% but not of further interest if the loco-regional control rate at one year was 50% or less. With the use of a two-sided test with 0.80 statistical power and a significance level of 0.05 the trial needed 85 eligible patients. To compensate for withdrawals, the target number was set to 90 patients. With the acquired 51 patients, the power of the trial is 0.58. The time-to-event was estimated with the Kaplan-Meier method. Loco-regional control rate was defined as the time from registration until loco-regional progression. Patients were censored at the last follow-up or at the date of death if they did not have any evidence of loco-regional failure. Progression-free survival was defined as the time from registration until progression or death from any cause. Overall survival was defined as the time from registration until death. Living patients were censored at the last follow up, approximately 36 months after registration. We used cox proportional hazard models for univariate and multivariate analysis of factors. Associations between categorical variables were tested with Fischer´s exact test and Chi-square test for association. The differences were considered significant at the 5% level ($p < 0.05$). Data were analysed with IBM SPSS Statistics for Windows, version 24.0 and Stata software, version 14.0.

4.2.8 Ethical considerations

The study was approved by the Research Ethics Committees Sweden (registration numbers 2010/414 and 2014/1978-32), Denmark (registration number H-1-2011-002) and Norway (registration number 2012/1382). All participating patients provided written informed consent.

5 RESULTS

5.1 PAPER I AND II

5.1.1 Enrolment and given treatment

Out of the 285 patients who were assessed for eligibility, 181 were randomised as displayed in Figure 11. Patients were recruited in nine cities in Sweden and Norway as detailed in Table 1. Baseline characteristics were well balanced between the treatment groups as displayed in Table 2.

Figure 11 *Flow chart of the NeoRes I trial*

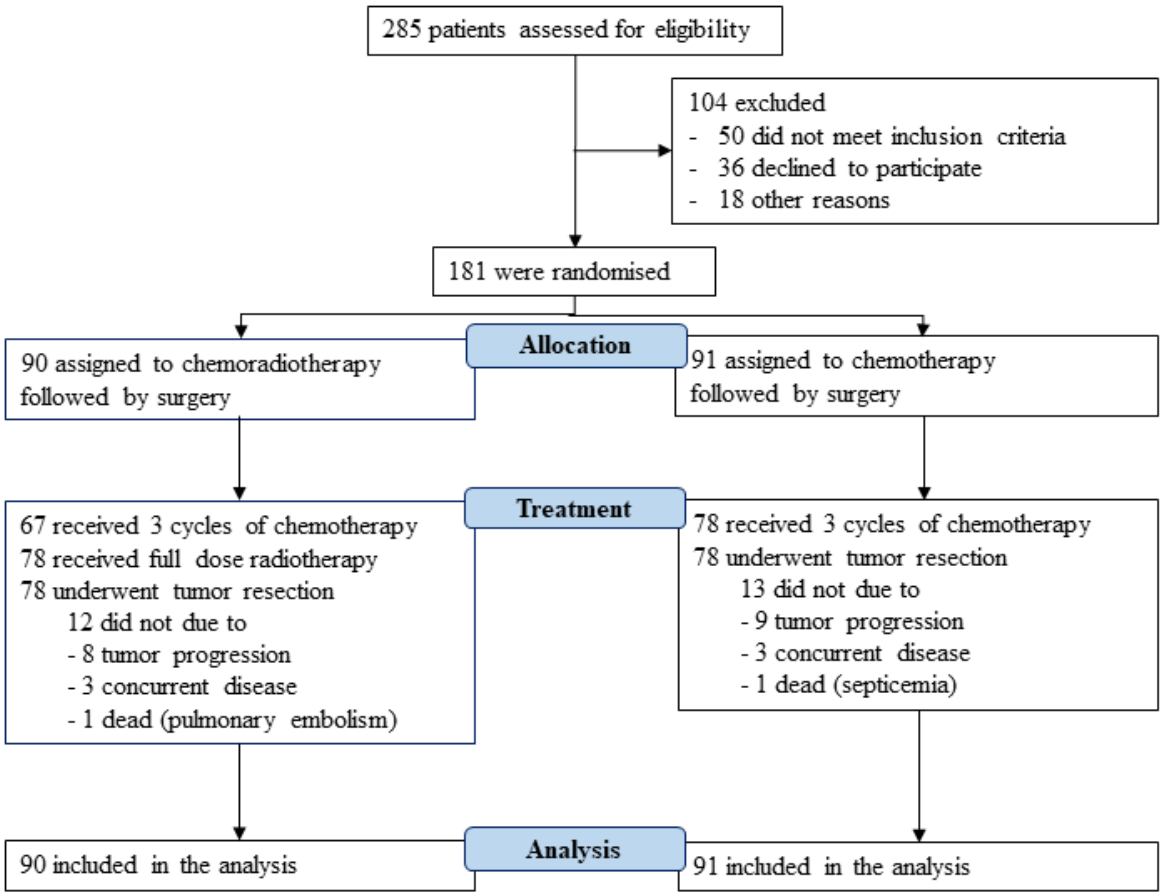


Table 1 *Patients included in Paper I and II by recruiting centre.*

Site	Number of patients
Stockholm (Radiumhemmet and Södersjukhuset)	77
Oslo (Ullevål and Radiumhospitalet)	32
Trondheim	24
Bergen	16
Umeå	15
Örebro	6
Eskilstuna	4
Göteborg	4
Karlstad	3

Table 2 *Demographic and disease-specific characteristics of patients enrolled in Paper I and II*

	Patients assigned to receive chemoradiotherapy	Patients assigned to receive chemotherapy
Median age (range)	63 (37-75)	63 (38-75)
Sex		
Male	72	77
Female	18	14
ECOG Performance status		
0	75	77
1	15	14
Histology		
Adenocarcinoma	65	66
Squamous cell carcinoma	25	25
Tumour location		
Proximal	2	2
Mid	13	13
Distal	60	59
Gastro-oesophageal junction	15	17
Clinical T-stage[a]		
1	1	1
2	31	31
3	58	59
Clinical N-stage[a]		
0	33	34
1	57	57

[a]American Joint Committee on Cancer tumour-nodes-metastasis staging system 6th edition
Abbreviation: ECOG = Eastern Cooperative Oncology Group

Treatment intensity was good, 91% of the patients in both treatment groups received at least two of the planned three cycles of chemotherapy and 87% of those allocated to chemoradiotherapy received full dose radiotherapy. Tumour resection rate was high, 87% in the chemoradiotherapy group and 86% in the chemotherapy group. The majority of patients were operated on with a thoraco-abdominal approach (Ivor Lewis or three-stage oesophagectomy). Details are presented in Table 3.

Table 3 *Delivered treatment in Paper I and II*

Delivered treatment	**Patients assigned to receive chemoradiotherapy (n=90)**	**Patients assigned to receive chemotherapy (n=91)**	**p-value**
Chemotherapy, 3 cycles	67 (74%)	78 (86%)	0.06[c]
Full dose radiotherapy	78 (87%)	1 (1%)[a]	
Surgical approach	78 (87%)	78 (86%)	0.85[c]
Ivor Lewis oesophagectomy	49 (63%)[b]	54 (69%)[b]	0.51[c]
Three-stage oesophagectomy	19 (24%)[b]	16 (21%)[b]	0.55[c]
Transhiatal oesophagectomy	8 (10%)[b]	7 (9%)[b]	0.77[c]
Total gastrectomy	2 (3%)[b]	1 (1%)[b]	0.62[d]
No resection	12 (13%)	13 (14%)	0.85[c]

Data are number of patients unless otherwise indicated
[a]One patient allocated to chemotherapy was accidently given 40 Gy
[b]Percent of those resected
[c]Chi-square test for association
[d]Fisher exact test

The number of serious adverse events did not differ between the treatment groups (p=0.14) as displayed in Table 4.

Table 4 *Serious adverse events in Paper I and II*

Serious adverse event	**Number of events among those assigned to receive chemoradiotherapy**	**Number of events among those assigned to receive chemotherapy**
Infection	5	5
Nausea and vomiting	6	2
Nutritional deficiency	13	13
Gastrointestinal symptoms	5	1
Cardiovascular event	14	7
Renal failure	4	7
Neutropenia/thrombocytopenia	5	2
Other	3	3
Death	2	1
Total number of serious adverse events	57	41

Data are number of patients unless otherwise indicated

A serious adverse event was defined as an event which
-required intervention to prevent permanent impairment
-required initial or prolonged hospitalization and did not include planned hospitalisation
-was disabling
-was life-threatening
-resulted in death

5.1.2 Pathological evaluation

Patients treated with chemoradiotherapy were more likely to respond with complete histopathological response, have a radical tumour resection and less likely to have lymph node-metastasis at resection than those treated with chemotherapy. Details are displayed in Table 5

Table 5 *Pathological evaluation of resected specimens in NeoRes I*

	Patients assigned to receive chemoradiotherapy (n=78)	**Patients assigned to receive chemotherapy (n=78)**	**p-value**
Tumour regression grade			<0.001
Grade I: Histological complete response	22 (28%)	7 (9%)	0.002
Grade II: 1-10 % residual carcinoma	19 (24%)	5 (6%)	
Grade III: 11-50% residual carcinoma	14 (18%)	5 (6%)	
Grade IV: >50% residual carcinoma	23 (29%)	61 (78%)	
Radical resection (R0)	58 (87%)	58 (74%)	0.042
Tumour-free longitudinal margin	77 (99%)	75 (96%)	0.31
Tumour-free circumferential margin	69 (88%)	60 (78%)	0.09
Viable lymph node metastasis at surgery	27 (35%)	48 (62%)	0.001

Data are number of patients unless otherwise indicated

A logistic regression was performed to ascertain the effects of treatment, age, performance status, sex, histology, clinical T- and N-stage on the likelihood to achieve complete histopathological response in the primary tumour. Patients with squamous cell carcinoma were 2.49 times more likely to respond with complete histopathological response than those with adenocarcinoma (p=0.049) and patients allocated to chemoradiotherapy were 3.92 times more likely to respond with complete histopathological response than those allocated to chemotherapy (p=0.005). We did not find any other baseline characteristics affecting the rate of histopathological response.

5.1.3 Survival

All patients were followed until death or at least 60 months after randomisation. In the survival analysis patients were censored at 60 months after randomisation. There was no difference in overall survival or progressions-free survival between those allocated to chemoradiotherapy and those allocated to chemotherapy as displayed in Figures 12 and 13. Median overall survival was 31.4 months (95% CI 20.9-60.0) in patients in the chemoradiotherapy group and 36.0 months (95% CI 22.4-59.6) in patients in the chemotherapy group. Overall survival at five years reached 42.2% (95% CI 31.9%-52.1%) in the chemoradiotherapy group and 39.6% (95% CI 29.5%-49.4%) in the chemotherapy group, p= 0.60. Progression-free survival at five years reached 38.9% (95% CI 28.9%-48.8%) in the chemoradiotherapy group and 33.0% (95% CI 23.6%-42.7%) in the chemotherapy group, p= 0.82.

Median overall survival was 30.8 months (95% CI 20.6-52.3) in patients with adenocarcinoma and 60.0 months (95% CI 23.7-60.0) in patients with squamous cell carcinoma, p=0.48.

Median progression-free survival was 19.5 months (95% CI 13.6-33.7) in patients with adenocarcinoma and 49.4% months (95% CI 20.9-60.0) in patients with squamous cell carcinoma, p=0.17.

Figure 12 *Overall survival by treatment group in the NeoRes I trial. Intention to treat.*

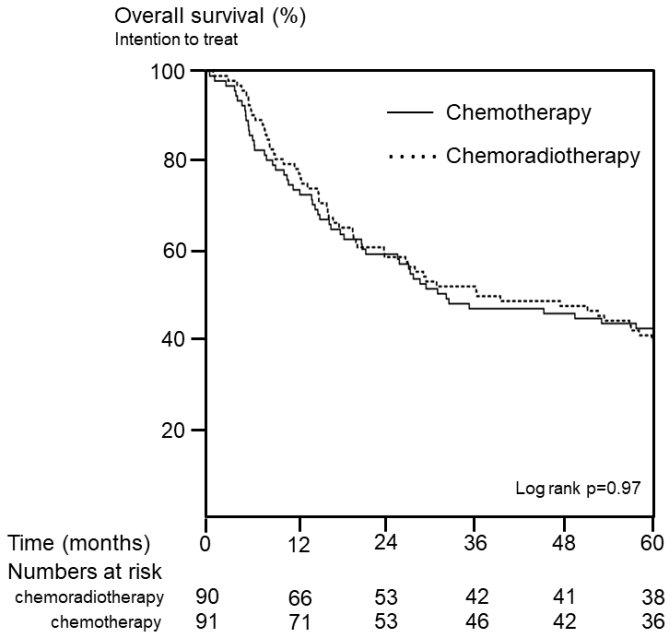
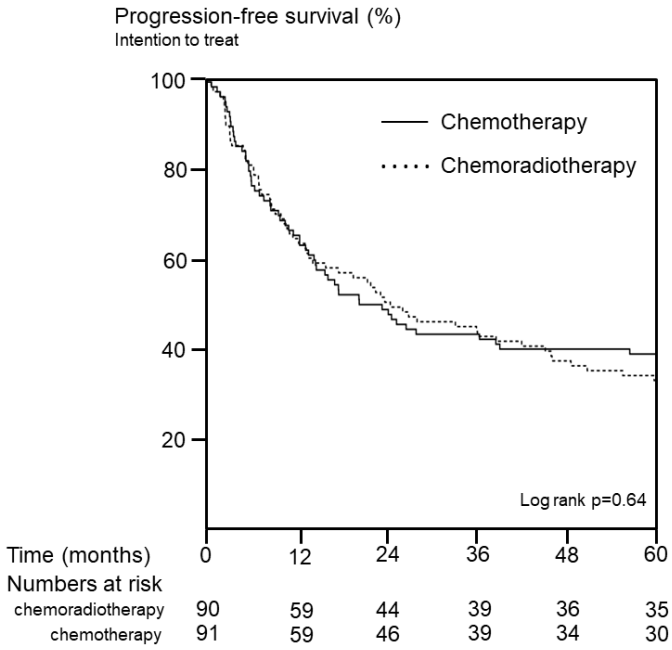
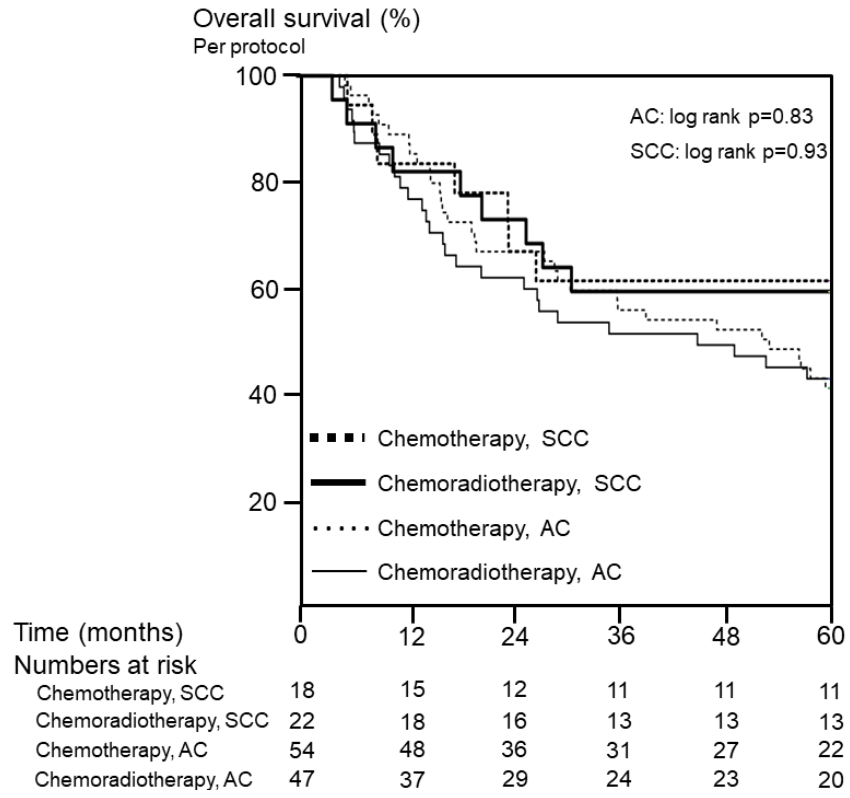


Figure 13 *Progression-free survival by treatment group in the NeoRes I trial. Intention to treat.*



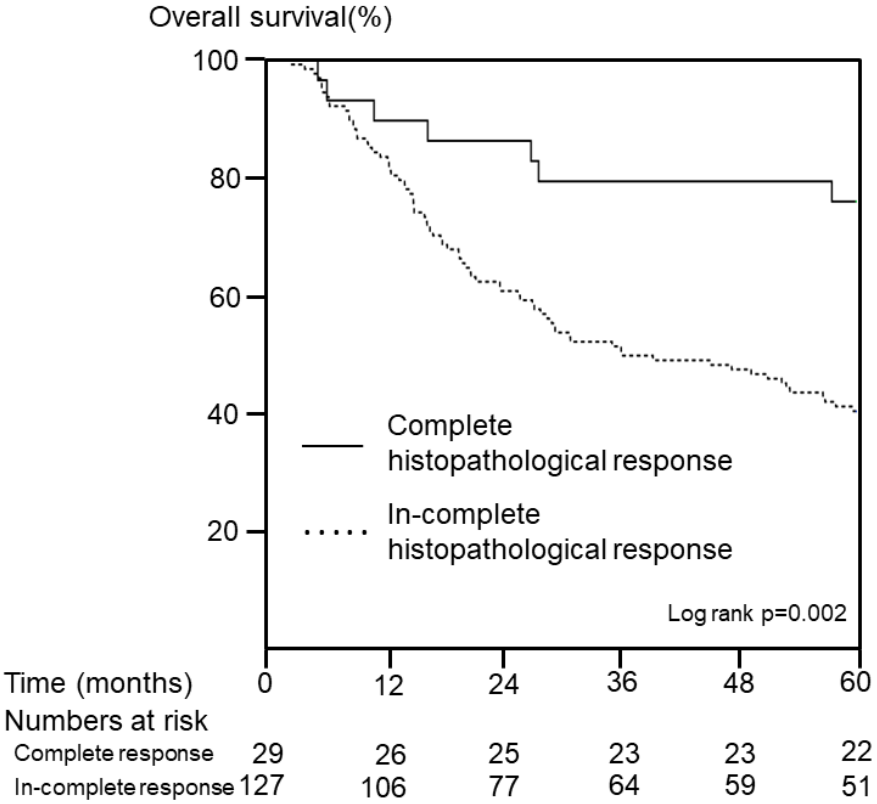
In the chemotherapy group 72 patients underwent tumour resection after at least two cycles of chemotherapy and no radiotherapy. In the chemoradiotherapy group 69 patients underwent tumour resection after at least two cycles of chemotherapy and at least 30 Gy. Among those, overall survival at five years was 47.8% (95% CI 35.7%-59.0%) in the chemoradiotherapy group compared to 44.4% (95% CI 32.8%-55.5%) in the chemotherapy group, p= 0.27. In this group of patients, referred to as the per protocol group, neither patients with adenocarcinoma nor patients with squamous cell carcinoma benefited from the addition of radiotherapy as displayed in Figure 14.

Figure 14 *Overall survival by treatment group and histology in the NeoRes I trial. Per protocol.*



Patients with complete histological response reached a five-year survival rate of 75.9 (95% CI 55.9%-87.7%) compared to 40.5% (95% CI 31.9%-48.9%) in those who did not achieve complete histological response, p< 0.001 as displayed in Figure 15.

Figure 15 *Overall survival by tumour response*



5.1.3.1 Impact of risk factors on overall survival

Baseline characteristics that could affect survival are listed in Table 6 which shows that female sex, lower clinical T-stage and squamous cell carcinoma tended to have a more favourable prognosis compared to male sex, higher clinical T-stage and adenocarcinoma.

Table 6 *The association between pre-treatment characteristics and overall survival*

	Number of patients	**Univariate analysis**		**Multivariate analysis**	
		Crude hazard ratio (95% CI)[a]	*p-value*	*Adjusted hazard ratio (95% CI)*[b]	*p-value*
Age					
≤60	66	1.00		1.00	
>60	115	1.06 (0.71-1.58)	0.78	1.03 (0.68-1.54)	0.90
Sex					
Male	149	1.00		1.00	
Female	32	0.56 (0.32-0.98)	0.04	0.57 (0.33-1.01)	0.05
ECOG Performance Status					
0	152	1.00		1.00	
1	29	0.71 (0.41-1.25)	0.24	0.66 (0.37-1.17)	0.16
Tumour location					
Cardia/distal	151	1.00		1.00	
Proximal/middle	30	1.05 (0.64-1.73)	0.84	1.39 (0.78-2.45)	0.26
Histology					
Squamous cell carcinoma	50	1.00		1.00	
Adenocarcinoma	131	1.40 (0.89-2.21)	0.15	1.69 (0.98-2.89)	0.06
Clinical T-stage					
1-2	64	1.00		1.00	
3	117	1.47 (0.97-2.23)	0.07	1.60 (1.01-2.54)	0.05
Clinical N-stage					
0	67	1.00		1.00	
1	114	1.20 (0.81-1.78)	0.37	1.16 (0.74-1.82)	0.52

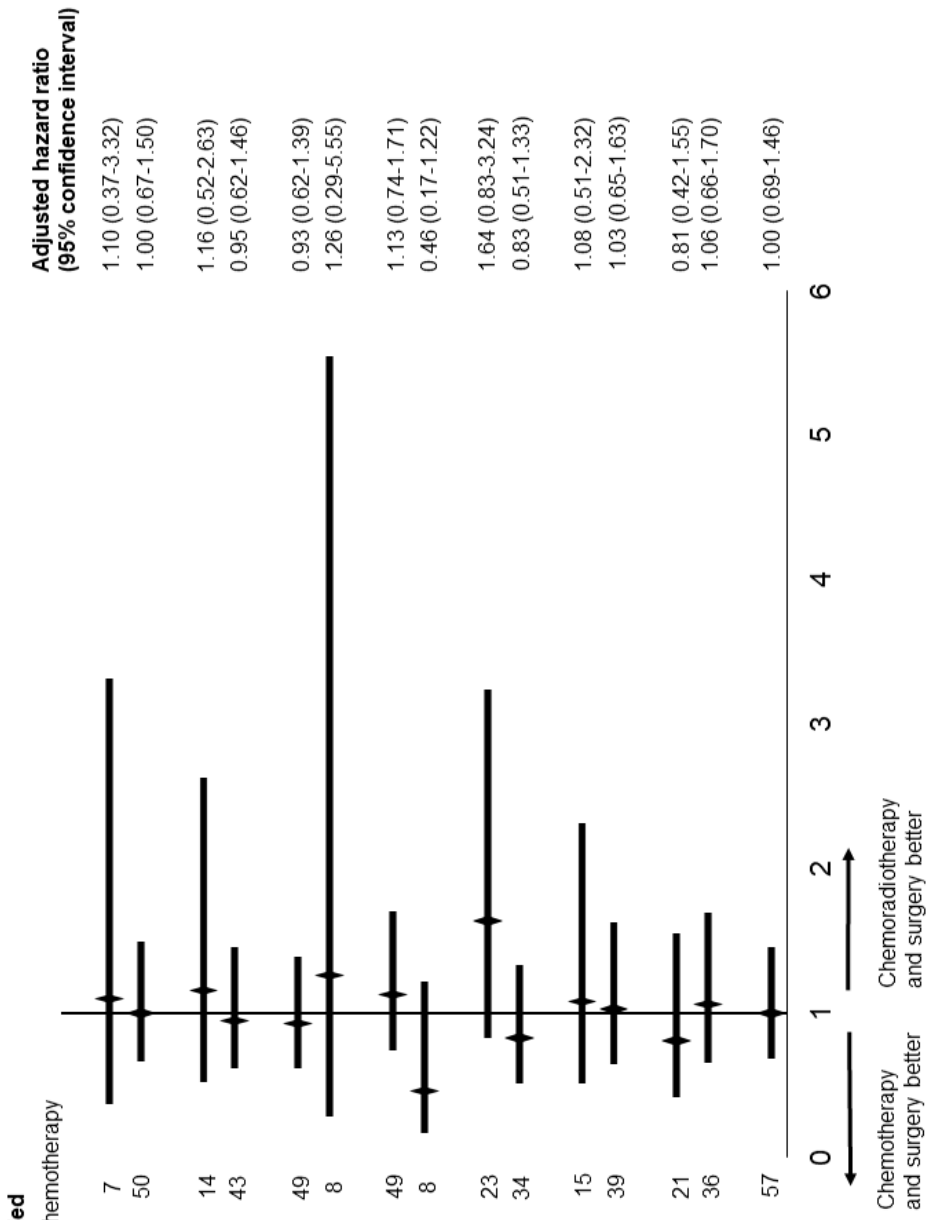
Abbreviation: CI; confidence interval. ECOG; Eastern Cooperative Oncology Group

[a] Crude hazard ratios and 95% confidence intervals were obtained using univariate Cox proportional hazard regression models.

[b] Adjusted hazard ratios and 95% confidence intervals were obtained using multivariate Cox proportional hazard regression models, adjusting for age, sex, performance status, tumour location, histology, clinical T- and N-stage.

As shown in Figure 16 none of the two treatment options seem to offer any advantage to a specific group of patients as specified by their different baseline characteristics.

Figure 16 *Cox regression analysis with adjustment for baseline variables to assess if certain patient groups had an increased likelihood of improved survival with chemotherapy or chemoradiotherapy.*



5.1.4 Patterns of recurrence

All recurrences were diagnosed with a CT, histology or both.

Potential prognostic factors predicting patterns of recurrence were analysed. We found no differences in frequency or patterns of recurrence between the treatment groups. Among patients who underwent tumour resection, 41 patients (53%) among those allocated to chemotherapy experienced a recurrence compared to 34 patients (44%) among those who were allocated to chemoradiotherapy (p=0.27). Potential prognostic factors predicting patterns of recurrence were analysed and no differences in frequency or patterns of recurrence between the treatment groups were seen. We found adenocarcinoma to be more prone to set early distant metastasis than squamous cell carcinoma. Details are in Table 7.

Table 7 *Potential prognostic factors for primary site of recurrence for patients who underwent tumour resection*

	Total number of patients (n=156)	**Locoregional recurrence with or without distant recurrence (n=38)**		**Distant recurrence with or without locoregional recurrence (n=60)**	
		Number of patients (%)	*Odds ratio (95% CI)*	*Number of patients (%)*	*Odds ratio (95% CI)*
Age					
≤60	59	18 (30.5%)	1.00	22 (37.2%)	1.00
>60	97	20 (20.6%)	0.55 (0.26-1.19)	38 (39.2%)	1.07 (0.52-2.19)
Sex					
Male	126	32 (25.4%)	1.00	52 (41.2%)	1.00
Female	30	6 (20.0%)	0.75 (0.29-2.14)	8 (26.7%)	0.50 (0.20-1.28)
ECOG Performance status					
0	132	35 (26.5%)	1.00	53 (40.2%)	1.00
1	24	3 (12.5%)	0.37 (0.10-1.36)	7 (29.2%)	0.50 (0.18-1.41)
Histology					
Squamous cell carcinoma	43	8 (18.6%)	1.00	11 (25.6%)	1.00
Adeno-carcinoma	113	30 (28.3%)	1.42 (0.57-3.51)	49 (43.3%)	2.72 (1.17-6.31)*
Clinical T-stage					
1-2	56	15 (26.8%)	1.00	16 (28.6%)	1.00
3	100	23 (23.0%)	1.09 (0.47-2.53)	44 (44.0%)	2.08 (0.93-4.63)
Clinical N-stage					
0	61	17 (27.9%)	1.00	19 (31.1%)	1.00
1	95	21 (22.1%)	0.79 (0.35-1.80)	41 (43.2%)	1.77 (0.82-3.85)
Allocated treatment					
Chemo-radiotherapy	78	18 (23.1%)	1.00	26(33.3%)	1.00
Chemo-therapy	78	20 (25.6%)	1.05 (0.50-2.22)	34 (43.6%)	1.59 (0.80-3.17)

Abbreviation: CI; confidence interval.
Odds ratio and 95% confidence intervals were obtained using multivariate unconditional logistic regression models, adjusting for age, sex, performance status, histology, clinical T and N-stage and allocated treatment.
* $p < 0.05$.

5.1.5 Causes of death in the NeoRes I trial

At the time of the final survival analysis 52 (58%) patients in the chemoradiotherapy group and 55 (60%) patients in the chemotherapy group had died. Among those allocated to chemoradiotherapy significantly more patients died from postoperative complications, of whom the last one died eight months after surgery. Details are specified in Table 8.

Table 8 *Cause of death*

Cause of death	Patients assigned to receive chemoradiotherapy (n=90)	Patients assigned to receive chemotherapy (n=91)	p-value
Oesophageal cancer	41 (46%)	47 (52%)	0.41[a]
Other disease	2(2%)	6 (7%)	0.28[b]
Post-operative complication	8 (9%)	1 (1%)	0.02[b]
Side effect from neoadjuvant treatment	1 (1%)	1 (1%)	1.00[b]
Total	52 (58%)	55 (60%)	0.72[a]

Data are number of patients unless otherwise indicated

[a]Chi-square test for association

[b]Fisher exact test

5.2 PAPER III

5.2.1 Enrolment and completed investigations

All patients randomised in the NeoRes I trial in Trondheim and Stockholm, except four in whom none of the results from spirometries or cardiac exercise tests could be retrieved, were included in the analysis reported in Paper III. Baseline characteristics of included patients are displayed in Table 9.

Table 9 *Baseline characteristics of patients enrolled in Paper III*

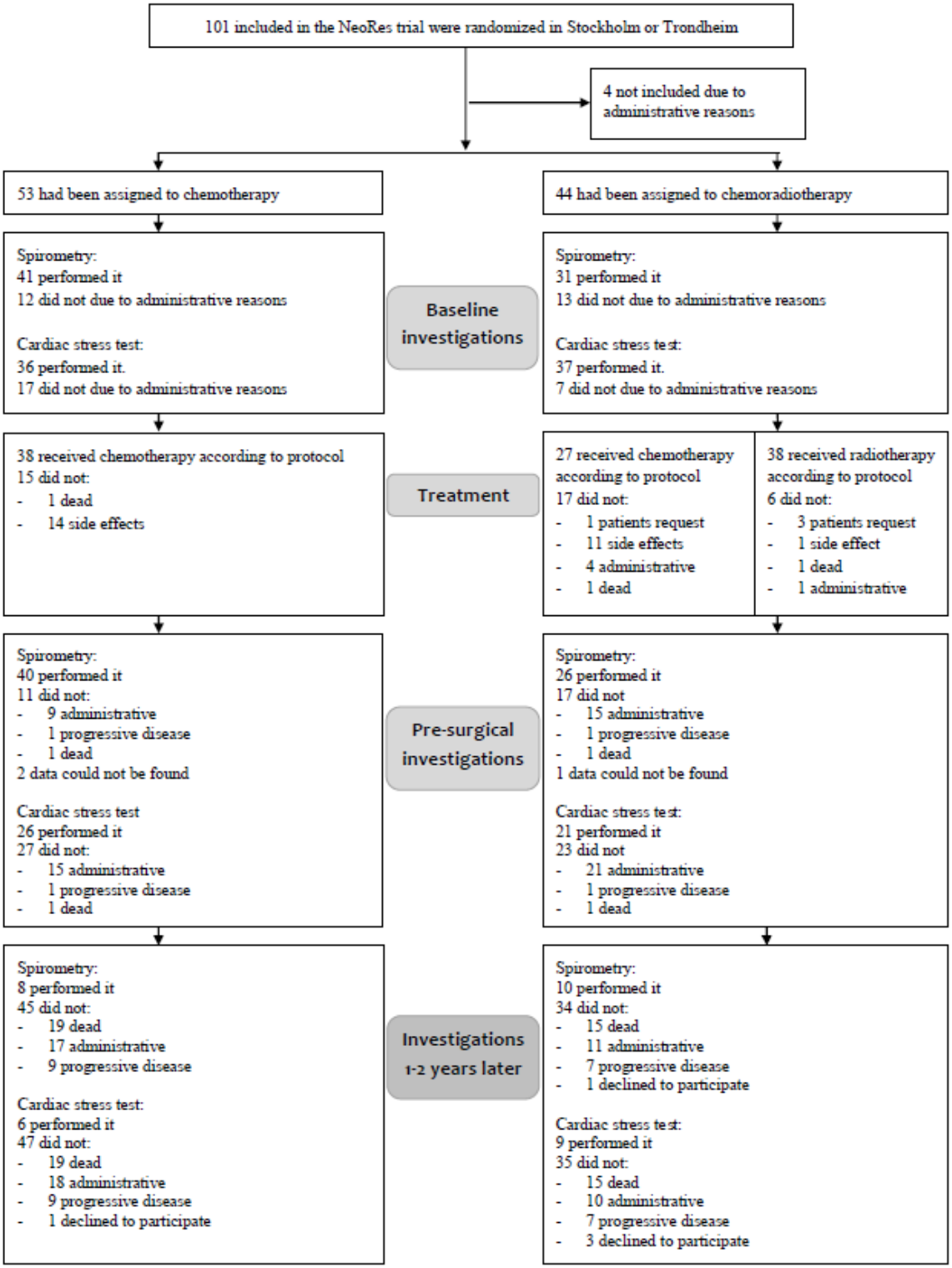
	Total	**Patients assigned to receive chemotherapy (n=53)**	**Patients assigned to receive chemoradiotherapy (n=44)**
Median age (years)		63	64
Sex			
Male	82	45 (85%)	37 (84%)
Female	15	8 (15%)	7 (16%)
WHO Performance Status			
0	88	47 (89%)	41 (93%)
1	8	5 (9%)	3 (7%)
unknown	1	1 (2%)	
Stage			
Stage II	30	16 (30%)	14 (32%)
Stage III	66	36 (68%)	30 (68%)
Stage IVa	1	1 (2%)	
Tumour location			
Proximal	1		1 (2%)
Mid	19	10 (19%)	9 (20%)
Distal	60	34 (64%)	26 (59%)
Cardia type II	17	9 (17%)	8 (18%)
Smoking			
Never smoked	13	5 (9%)	8 (18%)
Stopped smoking more than one year ago	25	15 (28%)	10 (23%)
Smoker	44	26 (49%)	18 (41%)
Unknown	15	7 (13%)	8 (18%)
Diabetes mellitus			
Yes	18	9 (17%)	9 (20%)
No	74	41 (77%)	33 (75%)
Unknown	5	3 (6%)	2 (5%)
Cardiovascular disease			
Yes	34	20 (38%)	14 (32%)
No	59	30 (57%)	29 (66%)
Unknown	4	3 (6%)	1 (3%)

Data are number of patients unless otherwise indicated

Of those assigned to chemotherapy, 77 % did the baseline spirometry and 68% did the baseline cardiac exercise test. The corresponding numbers for those assigned to chemoradiotherapy were 70% (baseline spirometry) and 84% (baseline cardiac exercise test).

In the chemotherapy group, 75% did the spirometry and 49% did the cardiac exercise test after oncological treatment. The corresponding numbers for the chemoradiotherapy group were 59% (spirometry) and 47% (cardiac exercise test). Of those assigned to chemotherapy 32% of living patients who had not been diagnosed with progressive disease did the long-term follow-up spirometry and 24% did the long-term follow-up cardiac exercise test. The corresponding numbers for those assigned to chemoradiotherapy were 45% (spirometry) and 41% (cardiac exercise test). Details are in Figure 17.

Figure 17 *Trial profile Paper III*



5.2.2 Treatment effects on pulmonary function

There was a slight decrease in pulmonary function from baseline until after oncological treatment. A more pronounced decrease was seen from baseline until the long-term follow-up where median values decreased with 7.4% (FEV1) and 14% (VC). In the eight patients that completed all three investigations, a gradual decrease was seen in VC but not in FEV1. Details are in Tables 9 and 10. All patients in the analysis who did the long-term follow-up had been resected using a thoraco-abdominal approach.

5.2.3 Treatment effects on cardiac exercise test

Maximum exercise capacity and blood pressure decreased from baseline until after neodadjuvant treatment. Median values decreased with 17% (maximum exercise capacity) and 13% (maximum blood pressure). From baseline until the long-term follow up the median values for maximum exercise capacity decreased with 16% and the median values for maximum blood pressure decreased with 15%. Twelve patients completed all three cardiac exercise tests and among those we found no further deterioration in recorded values from after neoadjuvant treatment until the long-term follow-up. When the maximum exercise capacity was adjusted for haemoglobin levels (by dividing the maximum exercise capacity with current haemoglobin values) we found no decrease from baseline until after neoadjuvant treatment, but from baseline until the long-term follow up the median value was decreased with 18%. We did not find any changes in the occurrence of significant arrhythmias or changes in the ST-segment on the electrocardiogram from baseline until later. Details from the cardiac exercise tests are in Tables 9 and 10. All patients in the analysis who did the long-term follow-up had been resected using a thoraco-abdominal approach.

Table 9 *Results from cardiac stress tests and spirometries, before and after neoadjuvant treatment*

	Before treatment Median (interquartile range)	After neoadjuvant treatment Median (interquartile range)	*p*-value *(Wilcoxon signed rank test)*	Number of patients
VC (l)	4.2 (3.5-4.8)	4.0 (3.0-4.8)	0.001	51
FEV1(l)	2.9[a] (2.6-3.5)	2.9[a] (2.3-3.4)	<0.001	
FEV%	73 (68-78)	73 (67-79)	0.609	
Max exercise capacity (W)	150 (125-175)	125 (103-153)	<0.001	47
Hb (g/l)	139 (129-149)	118 (108-129)	<0.001	
Max exercise capacity/hb (W/g/l)	1.09 (0.93-1.33)	1.10 (0.93-1.33)	0.697	
Max heart rate (/min)	152 (142-164)	149 (139-164)	0.158	47
Max blood pressure (mm Hg)	200 (170-210)	175 (150-200)	<0.001	42

[a]Median values are the same implicating that the reduction in pulmonary function is small.
Abbreviations: VC; Vital Capacity, FEV1; Forced Expiratory Volume in 1 second

Table 10 *Results from cardiac stress tests and spirometries, before the neoadjuvant treatment and 1-2 years later*

	Before treatment Median (interquartile range)	After 1-2 years Median (interquartile range)	*p*-value *(Wilcoxon signed rank test)*	Number of patients
VC (l)	3.7 (3.3-4.8)	3.2 (2.6-4.2)	0.005	11
VC (% of ref.value[a])	96 (75-103)	74 (65-85)	0.004	
FEV1 (l)	2.7 (1.9-3.0)	2.49 (2.0-2.7)	0.013	
FEV1 (% of ref.value[a])	89 (64-95)	69 (57-87)	0.007	
FEV%	71 (55-74)	70 (60-87)	0.120	
Max exercise capacity (W)	128 (115-170)	107 (80-125)	0.001	15
Max exercise capacity/hb (W/g/l)	0.97 (0.88-1.14)	0.80 (0.64-0.92)	0.017	
Hb (g/l)	138 (132-149)	134 (128-139)	0.065	
Max heart rate (/min)	153 (142-166)	142 (129-157)	0.002	
Max blood pressure (mm Hg)	200 (170-220)	170 (150-180)	0.012	

[a] reference values are adjusted by age, height and length
Abbreviations: VC; Vital Capacity, FEV1; Forced Expiratory Volume in 1 second, Hb; hemoglobin

5.2.4 Effects of radiotherapy on pulmonary function and cardiac stress test

Radiotherapy doses to the lungs and heart for patients who received 40 Gy are listed in Table 11. Due to a change in dose planning system in Stockholm, we did not retrieve doses to the lungs in nine patients and doses to the heart in seven patients.

Table 11 *Dosimetry data for patients who received 40 Gy*

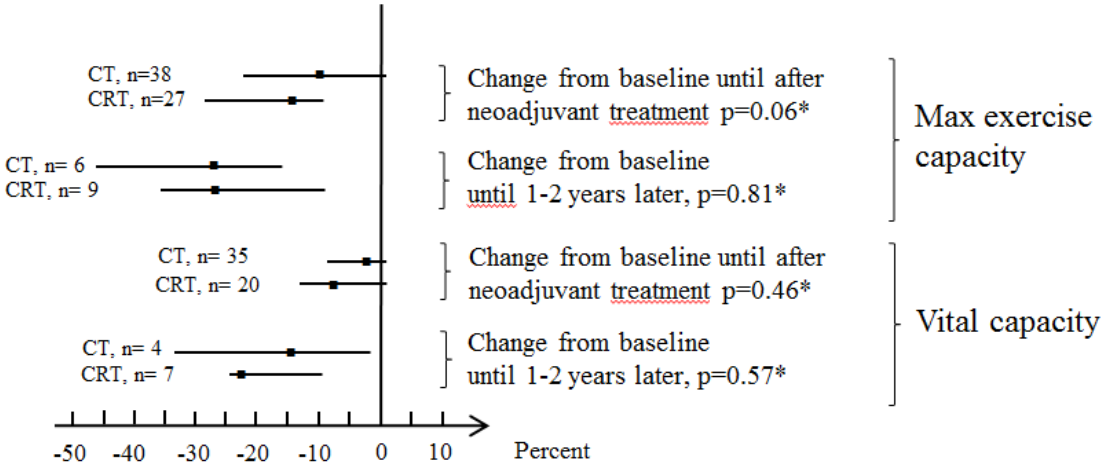
	Median (interquartile range)	**Number of patients**
Overall treatment time (days)	29 (26-30)	38
V20 lung[a] (%)	11.3 (8.1-16.2)	29
Mean lung dose (Gy)	8.8 (6.5-11.8)	29
V10 heart[b] (%)	80.0 (63.5-86.6)	31
V30 heart[c] (%)	41.4 (21.2-71.7)	31

[a]Volume of the lung receiving 20 Gy or more
[b]Volume of the heart receiving 10 Gy or more
[c]Volume of the heart receiving 30 Gy or more

We did not find any correlation between doses to the heart and changes in maximum exercise capacity. Neither did we find any correlation between doses to the lungs and the recorded changes in pulmonary function.

In our material the addition of radiotherapy to neoadjuvant chemotherapy did not further aggravate the decline in pulmonary function and exercise capacity as demonstrated in Figure 18.

Figure 18 *Maximum exercise capacity and vital capacity in patients receiving neoadjuvant chemotherapy or chemoradiotherapy*



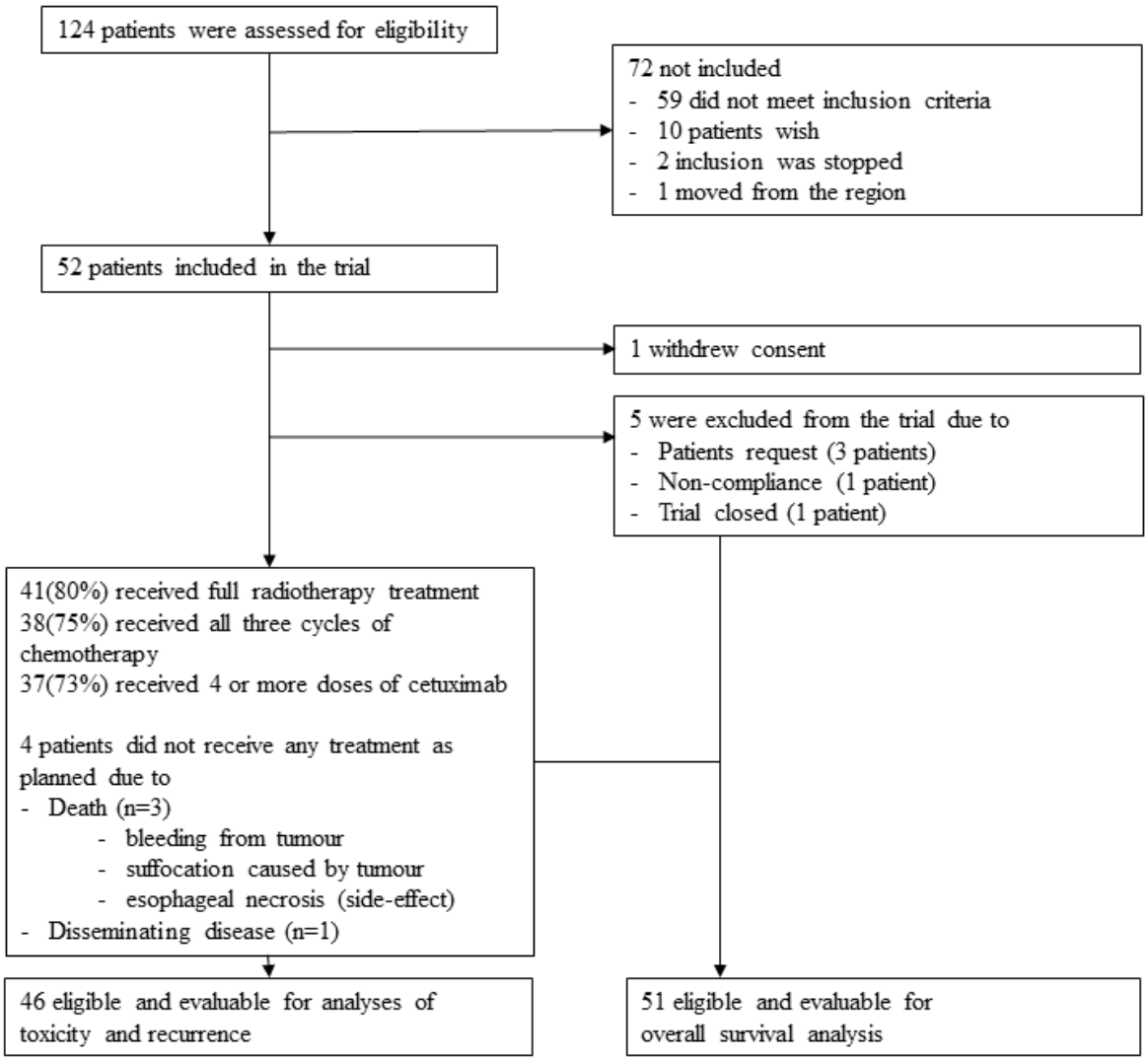
Dots represent median values. Lines show interquartile ranges.
n=number of patients
CT=Patients who received chemotherapy
CRT=Patients who received chemoradiotherapy
* Mann Whitney U test.

5.3 PAPER IV

5.3.1 Enrolment and delivered treatment

Between 2011 and 2014 we assessed 124 patients for eligibility in Sweden, Denmark and Norway whereof 52 were included of whom one later withdrew consent. Thereafter the trial was prematurely stopped when results from two randomised clinical trials could not prove any benefit from the addition of cetuximab to chemoradiotherapy in the treatment of oesophageal cancer. During treatment three patients died and one developed metastatic disease after one course of chemotherapy. 41 patients (80%) received full dose radiotherapy, 38 (75%) received all three courses of chemotherapy and 37 (73%) received at least four of the planned six doses of cetuximab. Median overall treatment time for the radiotherapy was 35 days for those who received 50 Gy (range 33-40 days). There was no significant difference in treatment intensity between those selected for non-surgical treatment due to medical unfitness than for those with non-resectable tumours (p=0.40). The trial profile is displayed in Figure 19.

Figure 19 *Flow chart of the LERFOX-C trial*



5.3.2 Adverse events

There were no un-expected adverse events with possible, probable or certain relation to given treatment. Related adverse events grade III and IV reported once were hyponatremia, pain, fatigue, rash, tinnitus, anaemia, neutropenia, septicaemia, elevation of cardiac troponin T, hypotension, syncope and pneumonitis. Those reported more than once are displayed in Table 12. Twenty-three patients (50%) experienced at least one related adverse event grade III and IV.

Table 12 *Related adverse events, grade III and IV during treatment, reported more than once in the 46 eligible patients.*

Adverse event	**Number of patients (%)**
Gastro-intestinal	16 (35)
Dysphagia	7 (15)
Anorexia	5 (11)
Oesophagitis	4 (9)
Mucositis	3 (7)
Nausea	2 (4)
Vomiting	2 (4)
Infection	6 (13)
Hypersensitivity	4 (9)
Pain	2 (4)

5.3.2.1 Fistulas

Within six months from the end of treatment, six patients died from complications from fistulas between the oesophagus and airways (three patients) or aorta (three patients). Five of the patients had been selected for definitive chemoradiotherapy due to local extent of tumour, and one due to medical unfitness. None of them had known fistulas before treatment. Five had received 50 Gy, and one received 38 Gy. All six patients had received at least four doses of cetuximab. In two patients there were microscopic tumour in the fistula at the post-mortem. In four of the patients post-mortems were not executed, but they had no clinical signs of tumour progression. Of those, two did a CT without radiographic signs of progression and one did an endoscopic examination without any macro- or microscopic findings of tumour. There was no significant association between pre-treatment dysphagia score or T-stage and fistula formation.

5.3.3 Response to treatment

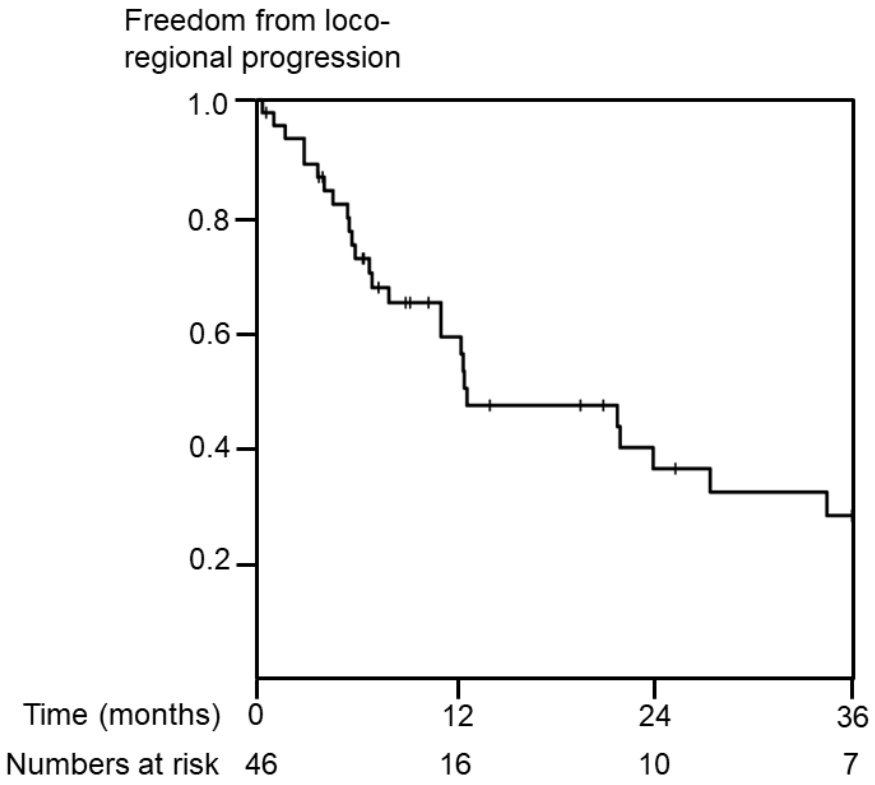
Among the 46 patients eligible for response evaluation, three died and one had tumour progression during treatment. Of the 42 remaining patients 26 (62%) responded to chemoradiotherapy partially (36%) or completely (26%). Ten (24%) had stable disease. All patients with at least stable disease were evaluated with a CT-scan or magnetic resonance tomography (MRT) which was supplemented with an FDG-PET in four patients and histology in three patients. We did not find any significant differences in response rate between patients with adenocarcinoma and squamous cell carcinoma. Three patients (20%) of those with a partial response and five (45%) of those with a complete response did not have a tumour recurrence during the study.

5.3.4 Recurrence

Four patients had disease progression and/or died during treatment. Of the remaining 42 evaluable patients, 16 (38%) had their first occurrence of progression in a distant site, six (14%) of whom had a concurrent loco-regional relapse. Isolated loco-regional relapse as first site of recurrence was noted in 19 (45%) patients, one of whom was successfully treated with oesophageal resection.

The probability of loco-regional control at one year was 47.3%, (95% CI 30.9% - 62.1%) as shown in Figure 20

Figure 20 *Loco-regional control in 46 evaluable patients*



Loco-regional control rate was better among those selected for definitive chemoradiotherapy because of cervical location of the tumour rather than local extent of the tumour. It also seems as though they had better loco-regional control than those not operated on due to medical unfitness, even though significance levels did not reach below 0.05. Details are in Table 13.

Table 13 *Baseline characteristics that might affect loco-regional control rate*

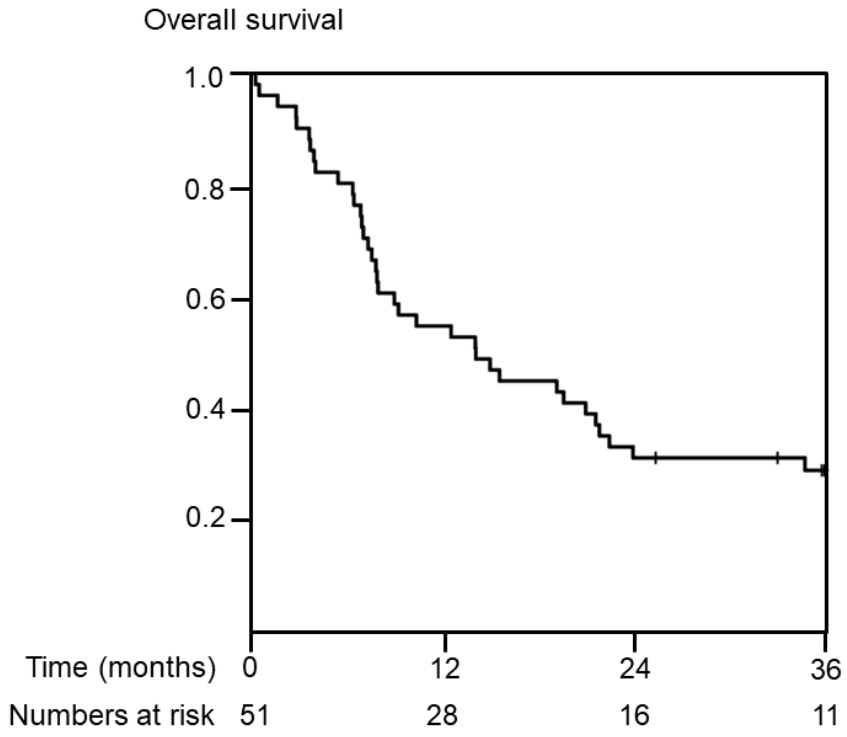
	Number of patients	**Univariate analysis**		**Multivariate analysis**	
		HR (95% CI)	*p*	*HR (95% CI)*	*p*
Age					
<70	32	1 (reference)		1 (reference)	
≥70	14	0.96 (0.40-2.30)	0.92	0.71 (0.26-1.95)	0.50
ECOG Performance Status					
0-1	40	1 (reference)	0.93	1 (reference)	
2	6	1.05 (0.36-3.06)		0.94 (0.26-3.38)	0.92
Body Mass Index					
<25	36	1 (reference)		1 (reference)	
≥25	10	0.95 (0.38-2.36)	0.90	1.27 (0.37-4.30)	0.71
Histology					
Adenocarcinoma[a]	9	1 (reference)		1 (reference)	
Squamous cell carcinoma[a]	36	0.68 (0.28-1.64)	0.39	0.83 (0.26-1.95)	0.50
Clinical T-stage					
2-3	21	1 (reference)		1 (reference)	
4	25	1.07 (0.49-2.32)	0.87	0.21 (0.03-1.26)	0.09
Reason for no resection					
Cervical location	12	1 (reference)		1 (reference)	
Local extent of tumour	23	3.15 (1.03–9.65)	0.05	14.05 (1.85–106.72)	0.01
Medically unfit	11	3.48 (1.03-11.75)	0.05	3.81 (1.00–14.58)	0.05

[a] One patient had adenosquamous carcinoma and is classified as missing.
The multivariate cox-regression analysis included the following baseline characteristics: age, ECOG performance status, Body Mass Index, histology, clinical T-stage and reason for no resection

5.3.5 Survival

The estimated overall survival at three years was 29.1% (95% CI 17.4-41.9%) for all 51 patients included in the trial. One patient was lost to follow-up after 25 months. The remaining patients were followed until death or three years after registration. Median overall survival was 14.0 months (95% CI 7.8-21.78 months). The survival curve is presented in Figure 21.

Figure 21 *Intention-to-treat analysis of overall survival.*



Progression-free survival for the 46 patients that were not excluded from the analysis was at three years 14.7%, (95% CI 6.2%-26.6%). Median progression-free survival was 6.7 months (95% CI 5.4-12.1 months).

In univariate and multivariate cox-regression analysis none of the covariates age, ECOG performance status, histology, T-stage or reason for non-resection were significantly associated with survival.

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Randomised and non-randomised clinical trials

A randomised trial is a study where the patients are divided by chance into separate groups after which a control intervention is compared to an experimental intervention. When initiating the trial, it is not known which intervention is the best with regard to the endpoints of the trial. A well-conducted randomised clinical trial is today considered to provide the highest level of scientific evidence. NeoRes I (papers I, II and III) is a randomised trial.

When new drugs are to be evaluated, clinical trials in different phases are conducted (Figure 22). LERFOX-C (paper IV) is a non-randomised phase II trial where the aim was to evaluate if the new drug, cetuximab, had an acceptable toxicity profile and worked well enough to test in a larger randomised trial in this particular group of patients. But, results from randomised trials prompted early termination of LERFOX-C and the results from LERFOX-C are to be regarded as confirmative.

Figure 22
Phases of a clinical trial

Phase I	Test of an experimental treatment with the aim to find the correct dosage and to evaluate safety and side effects.
Phase II	Test of an experimental treatment with the aim to obtain preliminary data on effectiveness and continuing study of safety and side effects. A phase II-trial may be randomised or not.
Phase III	Test of an experimental treatment in regard to safety and effectiveness compared to a standard of care treatment. A phase III-trial is most often randomised.
Phase IV	These trials aim to study long-term benefits and side effects. They usually take place after the new treatment has been approved by the healthcare authorities.

6.1.2 Validity

Validity in a scientific investigation means that the trial is accurately measuring what it claims to be measuring. It can be divided into internal and external validity.

6.1.2.1 Internal validity

The internal validity of any type of study is to what extent it is measuring what it claims to be measuring within the source population. The source population is determined by the inclusion and exclusion criteria for the participants in the trial. The internal validity is to a large extent determined by to what degree systematic errors are minimized. Systematic errors can be sub-divided into selection bias, information bias and confounding.

6.1.2.1.1 Selection bias

When conducting a trial, a selection of patients from a population is done. When there is a difference between the study-participants and the source population a selection bias is introduced. One of the best ways to avoid selection bias is to use random methods when selecting patients to intervention.

The NeoRes I trial (papers I, II and III) is a randomised controlled trial and no other study design gives the power to balance unknown prognostic factors at baseline. A prerequisite is that the allocation sequence is hidden to the investigators which was secured in the NeoRes I trial as the allocation was computerized and performed by an independent institution. However, in paper III many of the patients did not perform the intended investigations which could introduce a selection bias, as it might be that caregivers found some patients to be too exhausted to undergo investigations or on the contrary too well to justify the investigations.

The LERFOX-C trial (paper IV) is a non-randomised intervention trial where the risk of selection bias needs to be taken into account. In this trial an experimental drug is used in addition to conventional treatment. As physicians in general aim to tailor treatment for each individual patient there might be an unintended selection of patients in favour of patients that physicians believe the new treatment is best suited for. This effect is smaller when there are many participating centres and countries as in the LERFOX-C trial.

6.1.2.1.2 Information bias

When there are errors in the collection of data about study subjects it is called information bias or misclassification bias. Information bias can be further divided into non-differential and differential.

Non-differential information bias is unrelated to the endpoints of the study. In large clinical trials, such as NeoRes I and LERFOX-C, it is quite probable that there have been a few typing errors when filling in the case-report forms, when transferring data from paper to database, when extracting data to the statistical software and finally to the manuscript. These errors are in general random and will not cause a false association between exposure and outcome, but if there are a large amounts of errors a true association might be hidden. As several physicians, nurses and data-managers have checked the data in these trials, the risk of a large volume of errors are minimized.

Differential information bias is when the misclassification varies between the study groups so that the error differs between the groups, thus affecting an endpoint of the study differentially. This may cause false associations and is consequently seen as a very severe form of bias. For example, this could happen if the outcome is determined by subjective methods and the exposure is not blinded. There is some subjectiveness involved when differentiating between the histopathological grades II, III and IV in the NeoRes I trial. However, the examining pathologist was blinded to given treatment and the risk of differential bias was thereby eliminated.

6.1.2.1.3 Confounding

A confounder is a variable that is associated with both the exposure and the outcome resulting in an association of the wrong reason. Randomisation, as in the NeoRes I trial, is a powerful way to eliminate known and unknown confounding factors as it is likely that the groups will have similar distributions of confounders. Adjustment for known confounders can also be done with multivariate statistical models, as is the case in the NeoRes I and LERFOX-C trials.

6.1.2.2 External validity

External validity is the extent as to which results from a trial can be generalised to other populations that are sufficiently similar to the trial population.

In the NeoRes trial only patients younger than 76 years with good performance status and no severe co-morbidity were included. Results might therefore not be readily extrapolated to

elderly patients or patients with a worse general condition. Patients included in the LERFOX-C trial had a lower performance status than in the NeoRes I trial, but still there is an unneglectable amount of patients in the general oesophageal cancer population presenting with a worse performance status and results should be generalised with caution in aging patients and in patients with low performance status.

6.1.3 Random errors and precision

Random errors are in contrast to systematic errors unpredictable, and have no pattern. They can be reduced by increasing the sample size or repeating measurements and thereby precision is increased. The amount of random errors is estimated with confidence intervals and tested with p-values.

The NeoRes I trial was designed for detecting a difference in histopathological response which was achieved, but it was underpowered for the survival analyses. However, as the survival differences between the two treatments were so small, a potential difference in a much larger study population would probably be very slight. In paper III a cohort of patients in the NeoRes I trial was included and only a limited number of patients completed a full investigational programme, partly due to the high recurrence rate among patients with oesophageal cancer. Consequently, the risk of type II errors (where true differences are not detected) cannot be neglected. This could be avoided with a larger study population.

6.2 HISTOPATHOLOGICAL RESPONSE AND SURVIVAL

The primary objective of the NeoRes I trial was to evaluate the rate of histopathological complete response after chemotherapy with or without the addition of radiotherapy. We found that the addition of radiotherapy improved response rate in the primary tumour, the radical resection rate increased and the number of metastatic lymph nodes at resection decreased. These findings confirm results from the two previously reported trials from Germany and Australia in patients with adenocarcinoma of the oesophagus[63-65]. The better response rate was however not translated into better survival for those treated with chemoradiotherapy, which is consistent with the results from the Australian trial. On the contrary, in the German trial a gain in survival was seen that almost reached significant levels. There are slightly different chemotherapy regimens and radiotherapy doses in the trials, but the German trial with the seemingly best effect from the addition of radiotherapy used the lowest radiotherapy doses. On the other hand, less extensive surgery was used in the German trial as only 48% of the patients who underwent tumour resection were operated on with a thoraco-abdominal approach compared to 83% in the NeoRes I trial and 100% in the Australian trial. Therefore, a possible explanation for the lack of survival benefit despite better tumour tissue response could be that the addition of radiotherapy may not increase local tumour control when extensive lymph node dissection is used. A support of this hypothesis is that there were fewer loco-regional recurrences among those who received radiotherapy in the German trial which was not seen in the NeoRes I and the Australian trial when more extensive surgery was practiced. As far as we know, no corresponding comparative trials have been completed in patients with squamous cell carcinoma.

Nevertheless, complete histopathological response after neoadjuvant therapy is a well-established prognostic factor for survival in oesophageal cancer[25], which is also confirmed in the NeoRes I trial. It has previously been shown that there is a correlation between radiosensitivity and chemosensitivity in tumour tissue[102-104]. Consequently, a good pathological response in the primary tumour from chemotherapy is likely to become even better by the addition of radiotherapy, but with no survival benefit if followed by extensive surgery. However, a good tumour response at the primary site also indicates response on

peripheral micrometastases from chemotherapy and can partly explain why tumour response in the resected specimen is a prognostic marker for survival.

When surgery is not preceded by neoadjuvant treatment, patients with squamous cell carcinoma have worse survival expectancy compared to patients with adenocarcinoma[105]. On the contrary, in NeoRes I patients with squamous cell carcinoma were more likely to respond with complete histopathological response and also showed a trend toward better survival compared to patients with adenocarcinoma. Our results are similar to the results presented from the CROSS-trial where patients were treated with neoadjuvant chemoradiotherapy followed by surgery[29,46] suggesting that squamous cell carcinoma is more susceptible to current oncological treatment strategies than adenocarcinoma. These results could not be confirmed in the LERFOX-C trial as too few patients were included to evaluate survival differences between patients with different tumour histology.

In LERFOX-C where cetuximab in addition to definitive chemoradiotherapy was evaluated, the estimated 3-year survival in this high-risk group of patients was as high as 31%. In other reports of treatment with definitive chemoradiotherapy 3-year survival ranges from 12.5% to 45%[49,106-109]. As there are substantial differences in patient and tumour characteristics between the trials, comparison is to be made with caution. Survival in LERFOX-C compared to the NeoRes I trial was considerably worse, which to a large extent can be explained by higher tumour stage and worse general condition among included patients. Survival advantages from the addition of cetuximab to definitive chemoradiotherapy cannot be evaluated in a non-randomised trial such as the LERFOX-C trial other than in hypothesis-generating discussions. However, during the time of inclusion results from two randomised clinical trials were presented which could not prove any gain in survival from the addition of cetuximab in this group of patients.

6.3 SIDE EFFECTS

Treatment of oesophageal cancer with curative intent is toxic. The aim is always to give treatment that is more likely to benefit than to harm the patient. To be able to properly assess the risk versus benefits, a thorough understanding of potential side effects from the various treatment options is required.

In NeoRes I acute side effects were equally distributed between the treatment groups, although the reduction in maximum exercise capacity tended to be more pronounced after chemoradiotherapy than after chemotherapy and postoperative complications were more severe in the chemoradiotherapy group as shown in another publication from the group[110]. Also, when analysing causes of death, we found that patients treated with neoadjuvant chemoradiotherapy were more likely to die from postoperative complications. Similar results were reported from the German trial evaluating the addition of radiotherapy to neoadjuvant chemotherapy as hospital mortality was increased after chemoradiotherapy followed by surgery[63]. In a recent meta-analysis neoadjuvant chemoradiotherapy tended to increase postoperative mortality which was not seen after neoadjuvant chemotherapy, even though a direct comparison could not prove any difference between the two treatment options[111].

After neoadjuvant treatment we found that the maximum exercise capacity measured on a stationary bicycle was reduced and the reduction remained 1-2 years after the following tumour resection. Similar acute effects on exercise capacity after neoadjuvant chemoradiotherapy were reported by Liedman *et al.*[112], but could not be demonstrated after less intense neoadjuvant treatment as reported by Tatematsu *et al.*[113]. There are several possible explanations to the decline in exercise capacity. First it can be explained by a decrease in haemoglobin. After adjustment for haemoglobin levels we were unable to confirm the reduction in exercise capacity when assessed after neoadjuvant treatment.

However, 1 to 2 years later, haemoglobin levels were back to pretreatment values and could not explain the decrease in exercise capacity. Second, it can be caused by fatigue which is a well-known side effect from anti-cancer treatment. Third, the large surgical trauma may contribute to the long-term reduction in exercise capacity. Fourth, cisplatin, fluorouracil and radiotherapy are all well-known to have the potential to cause cardio-toxic side effects as described in section 2:2.

We also found pulmonary function to be reduced after neoadjuvant treatment. Before surgery the effects were small, and maybe not clinically significant. But, 1-2 years later after surgery the reduction was more pronounced. As is the case with exercise capacity, pulmonary function after oncological treatment for oesophageal cancer is not well-documented. In a previous report where 19 patients were treated with chemoradiotherapy with palliative or curative intent a reduction in pulmonary function was seen[114]. In another report, when using a less aggressive chemoradiotherapy regimen, no reduction in pulmonary function could be demonstrated[115]. Late effect on pulmonary function after multimodality treatment of oesophageal cancer has to our knowledge not previously been reported. But, surgery alone for oesophageal cancer[116,117] and chemoradiotherapy for lymphoma and breast cancer[84,118] have been shown to cause a long-lasting decrease in pulmonary function. Possible explanations to the decrease in pulmonary function are radiotherapy as discussed in section 2:2 and surgery, partly explained by the thoracotomy procedure[116]. To further enhance the complexity, there might be a co-variation between pulmonary function and exercise capacity[119].

We did not find any significant differences in maximum exercise capacity and pulmonary function between those who received neoadjuvant chemotherapy and those who received neoadjuvant chemoradiotherapy. Many patients did not undergo the investigations, and the lack of difference between the treatment groups might be explained by a type II error.

In LERFOX-C most patients had large tumours invading nearby organs and a performance status 1-2, and still as many as 80% received full dose radiotherapy and 75% received all three planned cycles of chemotherapy indicating that treatment was well tolerated. However, the vulnerability of these patients is illustrated by the fact that two patients died from tumour related factors during treatment and within six months from the end of treatment, as many as six patients died from complications from fistulas between the oesophagus and adjacent organs. The incidence of fistulas in LERFOX-C seems to be similar as reported from other trials after chemoradiotherapy in similar groups of patients[108,109,120]. Fistulas may develop after chemoradiotherapy when the tumour is susceptible for treatment and becomes necrotic. But, fistulas can also be the natural progression of the disease and it is often difficult to distinguish between the two. Risk factors for the development of fistulas are not well documented, but symptoms from pre-treatment stenosis have been found to be associated with fistula formation[120] and in a retrospective analysis low serum cholesterol has been shown to be associated with oesophago-aortic fistulas[121]. We did not find T4-disease or pre-treatment stenosis measured as dysphagia score to be risk factors for fistula formation which could well be attributed to the small number of patients in our trial. From our data we cannot rule out that cetuximab contributed to the development of fistulas, but in the two randomised clinical trials evaluating the addition of cetuximab to chemoradiotherapy an increased incidence of fistulas was not reported[70,71].

During the time of inclusion in the NeoRes I trial and the LERFOX-C trial minimal invasive surgical techniques with endoscopic methods have been developed, less aggressive chemoradiotherapy regimens such as the CROSS regimen have been introduced and radiotherapy techniques such as VMAT have been developed where doses to the heart and lungs can be reduced. With this, side effects might be reduced in future patients.

6.4 RECURRENCE PATTERNS

Among evaluable patients in the LERFOX-C trial that did not die or progress during treatment, 83% experienced a tumour recurrence during the time of follow up. The corresponding number in the NeoRes trial was 48%. The large majority of patients included in the LERFOX-C trial experienced a loco-regional recurrence which was not seen in the NeoRes I trial. This can be explained by a larger number of patients with T4 disease and a less aggressive local treatment in the LERFOX-C trial as most patients did not undergo oesophageal resection.

The risk of loco-regional recurrence after definitive chemoradiotherapy is high, and data from LERFOX-C seem to be similar as those reported by Stahl *et al.*[107]. However, it seems as though patients selected for non-surgical treatment due to cervical location of the tumour rather than patient-related factors had a better loco-regional tumour control. Cervically located tumours in the oesophagus are preferably treated with non-surgical methods as it increases the chance of larynx preservation without decreasing the chance of survival[122] As their general condition is not the main reason to abstain from surgery, they are more likely to tolerate chemoradiotherapy than patients selected for non-surgical treatment due to medical unfitness, and this could explain the differences in tumour control in the LERFOX-C trial. Also, it has previously been shown that patients selected for non-surgical treatment due to un-resectable tumours are less likely to have a long-term benefit from treatment than those selected for non-surgical treatment due to patient-related factors[108]. Correspondingly, we found that patients selected for non-surgical treatment due to cervical location of the tumour had better prognosis than those with un-resectable tumours. However, the assessment of loco-regional relapse is challenging. In LERFOX-C the evaluation was primarily done using a CT-scan which is a draw-back of the trial as more accurate results could have been retrieved if a PET-scan and biopsies were done on all patients.

In the NeoRes I trial, the differences in tumour biology between squamous cell carcinoma and adenocarcinoma are highlighted in the recurrence patterns as distant metastases were more common as first site of recurrence in patients with adenocarcinoma. In LERFOX-C the number of included patients were too small to evaluate such differences, but the same patterns of recurrence was found by Xi *et al*. in patients treated with definitive chemoradiotherapy[123].

7 CONCLUSIONS

The addition of radiotherapy to neoadjuvant chemotherapy in the treatment of oesophageal and junctional cancer increases the rate of complete histopathological response and radical resection and also decreases the number of metastatic lymph nodes in the resected specimen. However, despite better tumour response, there was no gain in survival. Consequently, results from the NeoRes I trial do not support unselected addition of radiotherapy to neoadjuvant chemotherapy as standard of care.

The addition of radiotherapy to neoadjuvant chemotherapy does not affect frequency or patterns of recurrence.

Multimodality treatment of resectable oesophageal cancer causes short-term and long-lasting impairment in pulmonary function and exercise capacity.

Even in high-risk patients, oxaliplatin, fluorouracil and cetuximab given concurrent with radiotherapy was well tolerated and has a curative potential in localized oesophageal carcinoma. But, based on results from phase III trials the addition of cetuximab cannot be recommended as standard of care.

There is a substantial risk of fistula formation after treatment with definitive chemoradiotherapy in patients with oesophageal cancer.

8 FUTURE PERSPECTIVES

The NeoRes I trial adds to the growing evidence that squamous cell carcinoma and adenocarcinoma of the oesophagus are two different disease entities and are likely to benefit from different treatment strategies. Squamous cell carcinoma seems to be more susceptible to oncological treatment than adenocarcinoma and it might be that patients with squamous cell carcinoma can be spared surgery provided that tumour response can be assessed in a reliable way. In our research network we are planning a randomised trial comparing surgical resection with surveillance and rescue surgery in patients with complete response after chemoradiotherapy

Over the last 40 years, treatment with curative intent of oesophageal cancer have evolved tremendously with the evolution of chemotherapy, radiotherapy and better surgical techniques. Still survival is poor, which is also visualized by results from the trials in this thesis. Immunotherapy is a more recent way of targeting tumours, where the immune system is stimulated to produce an anti-tumour response. Quite likely there will be a role for immunotherapy also in the treatment of oesophageal cancer. Questions that need an answer are who will benefit from the treatment and in what way immunotherapy is to be combined with other therapeutic alternatives. There are numerous ongoing trials addressing these questions, and within our Scandinavian research network (SEGCG) an investigator-initiated trial, INEC, recently started.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund

Cancer i matstrupen är i västvärlden en ovanlig sjukdom. I Sverige insjuknar ca 500 personer per år. Sjukdomen ger sällan besvär i tidiga stadier vilket gör att cancern oftast är långt gången när den upptäcks och prognosen är förhållandevis dålig. Behandling med botande syfte kan ges om cancern inte har spridit sig till andra organ i kroppen och kan ges på tre sätt: (1) cytostatika samtidigt med strålbehandling, (2) cytostatika med eller utan samtidig strålbehandling följt av kirurgi eller (3) enbart kirurgi. Behandling med botande syfte är krävande och ger sidoeffekter. Syften med denna avhandling är att utvärdera effekter och sidoeffekter av behandling som ges med botande syfte till patienter med cancer i matstrupen.

Metodbeskrivning

Tre av fyra delarbeten i avhandlingen baseras på en Skandinavisk studie, NeoRes I. Patienterna i denna studie lottades till att få behandling med cytostatika med eller utan tillägg av strålbehandling följt av kirurgiskt avlägsnande av tumören.

Det fjärde delarbetet är en sammanställning av resultat från en annan Skandinavisk studie, LERFOX-C. Patienterna i denna studie hade cancer i matstrupen där kirurgi av olika skäl bedömdes olämpligt. Behandlingen bestod av cytostatika, strålbehandling och cetuximab (en antikropp).

Resultat

181 patienter inkluderades i NeoRes I. Studien visade att patienter som utöver cytostatika även fick strålbehandling före kirurgi hade färre cancerceller i den bortopererade matstrupen än de som fick enbart cytostatika före kirurgi. Den mer intensiva behandlingen gav ingen överlevnadsvinst. Fem år efter att behandlingen påbörjats levde cirka 40% av patienterna oavsett vilken behandling de hade fått.

Drygt hälften av patienterna som var med i NeoRes I var med i en delstudie där vi fann att lungfunktionen försämrades något och arbetskapaciteten försämrades markant efter cytostatika och strålbehandling. På lång sikt, 1-2 år senare, när patienterna även gått igenom en operation försämrades lungfunktionen ytterligare, och arbetskapaciteten var fortfarande påtagligt nedsatt.

I LERFOX-C deltog 51 patienter. De hade sämre allmäntillstånd och mer avancerade tumörer än i NeoRes I. Av dem vi hade möjlighet att undersöka hade 47% inte fått tillbaka cancern i matstrupen efter ett år. Efter tre år levde 29% av patienterna.

Slutsatser

Resultaten från NeoRes I stöder inte rutinmässigt tillägg av strålbehandling till cytostatika som ges före operation av matstrupscancer.

På kort sikt försämrar cytostatika och strålbehandling lungfunktion och arbetskapacitet hos patienter med matstrupscancer. På lång sikt, efter att patienterna också opererats, är försämringen fortsatt märkbar.

Resultaten från LERFOX-C bekräftar resultat från tidigare studier att cytostatika, strålbehandling och cetuximab kan bota patienter med matstrupscancer. Andra större studier har dock visat att tillägget av cetuximab inte förbättrar behandlingseffekten och kan därför inte rekommenderas.

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